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Optimization of influenza antiviral response in Texas

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OPTIMIZATION OF INFLUENZA ANTIVIRAL RESPONSE IN TEXAS

by

Travis L. Chambers

March 2015

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Influenza pandemics pose a serious threat to the global population. According to the United States Department of Health and Human Services in 2014, the Spanish flu of 1918 killed almost 100 million people worldwide and Simonsen, Spreeuwenberg, and Lustig in 2013 estimated that the Swine flu more recently killed approximately 180,000 people. Government agencies, from the United States Centers for Disease Control and Prevention down to state and local regions, are prepared to respond to potential influenza pandemics with antiviral, vaccine, and social interventions. Mathematical models can guide policies to saves lives. In this thesis, we create an optimization model, implemented in the online tool Texas Antiviral Release Scheduling (TAVRS) that provides the optimal geo-temporal antiviral release schedule to advise decision makers at the Texas Department of State Health Services. We input the antiviral release schedule into an independent disease-spread simulation model to measure the effectiveness of the optimal release schedule. While the TAVRS optimal antiviral release schedule performs comparably to a simple population-proportionate release schedule during a simulated mild 2009-like influenza pandemic, the TAVRS release schedules saves an additional 10,000 lives—three to four times greater—than the population-proportionate release schedule when responding to a severe 1918-like influenza pandemic.

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OPTIMIZATION OF INFLUENZA ANTIVIRAL RESPONSE IN TEXAS

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ABSTRACT

Influenza pandemics pose a serious threat to the global population. According to the United States Department of Health and Human Services in 2014, the Spanish flu of 1918 killed almost 100 million people worldwide and Simonsen, Spreeuwenberg, and Lustig in 2013 estimated that the Swine flu more recently killed approximately 180,000 people. Government agencies, from the United States Centers for Disease Control and Prevention down to state and local regions, are prepared to respond to potential influenza pandemics with antiviral, vaccine, and social interventions. Mathematical models can guide policies to saves lives. In this thesis, we create an optimization model, implemented in the online tool Texas Antiviral Release Scheduling (TAVRS) that provides the optimal geo-temporal antiviral release schedule to advise decision makers at the Texas Department of State Health Services. We input the antiviral release schedule into an independent disease-spread simulation model to measure the effectiveness of the optimal release schedule. While the TAVRS optimal antiviral release schedule performs comparably to a simple population-proportionate release schedule during a simulated mild 2009-like influenza pandemic, the TAVRS release schedules saves an additional 10,000 lives—three to four times greater—than the population-proportionate release schedule when responding to a severe 1918-like influenza pandemic.

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LIST OF ACRONYMS AND ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CFR	case fatality rate
DSHS	Department of State Health Services
FIPS	federal information processing codes
GA	genetic algorithms
GAMS	general algebraic modeling system
GUI	guided user interface
HHS	health and human services
HSR	health service regions
IHR	International Health Regulations
ILI	influenza-like illness
MIP	mixed integer linear program
NHTS	National Household Travel Survey
NI	neuraminidase inhibitors
PIPOG	Pandemic Influenza Plan Operational Guidelines
POV	personally operated vehicle
QALY	quality adjusted life years
RMHC	random mutating hill climbing
SEIR	susceptible, exposed, infected, recovered
SIR	susceptible, infected, recovered
SNS	Strategic National Stockpile
TAVRS	Texas Antiviral Release Scheduling
TPFS	Texas Pandemic Flu Simulator
UCT	upper confidence bounds applied to trees
WHO	World Health Organization

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EXECUTIVE SUMMARY

Pandemic influenza poses a significant threat to the populations of the world. Through the past century, four global influenza pandemics and a severe influenza epidemic have shown that the world is not fully prepared to respond to pandemic influenza, especially a severe strain such as the 1918 Spanish flu. Over one-fifth of the world's population is believed to have been infected with Spanish flu (Billings, 2005), and, 50 to 100 million people are thought to have died from Spanish flu or secondary complications incurred from the disease (U.S. Department of Health & Human Services, 2014). As recently as 2009, Swine flu caused approximately 180,000 deaths worldwide (Simonsen, Spreeuwenberg, & Lustig, 2013).

The World Health Organization (WHO) provides guidance to countries and international organizations and the Centers for Disease Control and Prevention (CDC) coordinates the national effort to respond to pandemic influenza (CDC, 2013). However, the burden of pandemic response falls on the state and local agencies to implement pandemic controls and interventions. Vaccinations are the most effective intervention, but they need time to develop and distribute. Until vaccines are available, the best response to pandemic influenza is a combination of social control measures, such as school closures and quarantine, and antivirals (Texas Department of State Health Services, 2008). Even in developed countries, antivirals are limited in number when compared to the requirements of a severe strain of influenza (Texas Department of State Health Services, 2008). The Texas Department of State Health Services (DSHS) has outlined a response strategy that includes antivirals, however it needs improvement from updated disease spread and intervention models. The Texas Pandemic Flu Toolkit provides decision makers in the state of Texas with critical disease spread information and response advice. Included in the toolkit, the Texas Pandemic Flu Simulator is a powerful compartmental disease spread model with time, location and demographic dimensions.

In our thesis, we develop an optimization program that is implemented in an online tool called Texas antiviral release scheduling (TAVRS), included in the Texas Pandemic Flu Toolkit, to provide the optimal allocation of antivirals to decision makers.

The optimization program includes time, location, and age-demographic dimensions. The optimization program targets the average treatable population during an influenza pandemic. The treatable population is the number of individuals at a certain location and time that have been symptomatic with influenza for less than 24 hours. Stochastic variations of historical influenza strains and geographic origins in Texas from the Texas Pandemic Flu Simulator are averaged to create this input into the optimization program. We formulate a mixed integer linear program to determine geo-temporal antiviral release schedule to maximize the benefit of available antivirals. We consider three benefits of antivirals: lives saved, hospitalizations avoided, or quality adjusted life years (QALY) saved.

We first consider a base case scenario, which consists of a 1918-like random-origin influenza pandemic with unlimited antivirals. The release schedule maximized the lives saved to roughly 26,500 by releasing a large amount immediately before the rise in treatable people. Although 30 million antivirals are available, TAVRS releases only 14 million. Antivirals are released to the highest populated counties during the weeks that precede the fast rise in treatable population. Antivirals released earlier may be consumed by the worried-well and antivirals released later are not available for the rise in treatable people.

Next, we examine several variants from the base model. When the pandemic originates near the border, the optimal schedule releases antivirals to the counties immediately prior to when the disease significantly spreads to them. When the pandemic originates in a highly populated county, the pandemic can spread quickly. A less virulent pandemic strain generates an extended release schedule duration and fewer antivirals released. A smaller supply of antivirals results in a delay in the release of the bulk of the antivirals. Finally, the specific objective function (lives saves, hospitalization, QALYs) had no apparent impact of the release schedule of antivirals.

Our analysis concludes with a comparison of the lives saved between the TAVRS antiviral release schedules and a simpler population-proportionate population distribution. The comparison found that in response to a mild pandemic, like the 2009 swine flu, the population-proportionate antiviral release schedule worked comparably the

TAVRS antiviral release schedule. However, in response to a severe strain of influenza, like the 1918 Spanish flu, the TAVRS antiviral release schedule performed drastically better saving roughly 10,000 more lives, three to four times greater, than the population-proportionate release schedule.

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I. INTRODUCTION

A. OVERVIEW

Infectious disease pandemics, in particular the highly contagious and unpredictable strains of influenza, pose a large and immediate threat to the peoples of the world. Influenza is a common and easily transmitted disease. Every year flu vaccines are provided by governmental organizations in the expectation of endemic influenza, an often-milder form of influenza occurring periodically throughout the winter in denser populations. Yet the possibility of an epidemic outbreak, in which the disease infects a more widespread population at a given time, constantly looms. An epidemic can expand to pandemic scale if the disease affects a large proportion of the worldwide population, which has the potential for massive numbers of deaths and catastrophic economic impacts. The capability of a pandemic strain of influenza to quickly grow and infect large populations makes it a considerable threat.

Government organizations prepare each year not only for the regularly occurring endemic influenza, but also for the possibility of a larger epidemic or pandemic strain. Counties and states develop vaccines for the most probable strains and prepare response plans for antivirals, vaccines, and social interventions. Many of them have turned to mathematical models to better predict and respond to pandemic influenza. Current advances in computing power and modeling algorithms have enabled states and countries to prepare better than ever for a worldwide pandemic. Coupled with the proper policy and resources, these models have the potential to minimize the cost of response and, most importantly, the loss of life in the case of an outbreak of pandemic influenza. This thesis seeks to develop a mathematical model to release antivirals most effectively in response to pandemic influenza in Texas.

B. MODERN ERA PANDEMICS

The influenza virus has afflicted human populations from the beginning of our existence. Modern times have seen no decrease in pandemics. Since 1918, there have been four global influenza pandemics, each with unique characteristics in epidemiology and disease severity (U.S. Department of Health & Human Services, 2014). Even with advances in medicine during the 20th century, the world was unable to prevent the severe loss of life. Today, the possibility of a pandemic strain of influenza sweeping through the highly connected populations of the world is a real fear for countries and states.

1. Spanish Flu (1918–1919)

The disease known as Spanish flu appeared shortly after World War I and quickly escalated into a worldwide pandemic. After one of the most brutal and gruesome wars to date, the Spanish flu emerged to infect almost one-fifth of the world's population (Billings, 2005). The strain of influenza called Spanish flu is considered Influenza A (H1N1). It was known for its extremely high case fatality rate (CFR), which was upwards of 2.5 percent in certain segments of the population (Billings, 2005).

From 1918 to 1919, the disease traversed the globe in three separate waves, each affecting a region of the world for up to 12 weeks and then dissipating (Taubenberger & Morens, 2006). The graph in Figure 1 shows the mortality of the three distinct waves as they swept through Great Britain. The first wave arrived in March of 1918 and swept through Europe, the United States, and Asia throughout the following six months (Taubenberger & Morens, 2006). The illness rates were high, but deaths due to the flu were not. The second wave that was the most deadly, peaking at almost 25 deaths per 1000 people from September to November of 1918 (Taubenberger & Morens, 2006). Finally, the third wave occurred early in 1919.

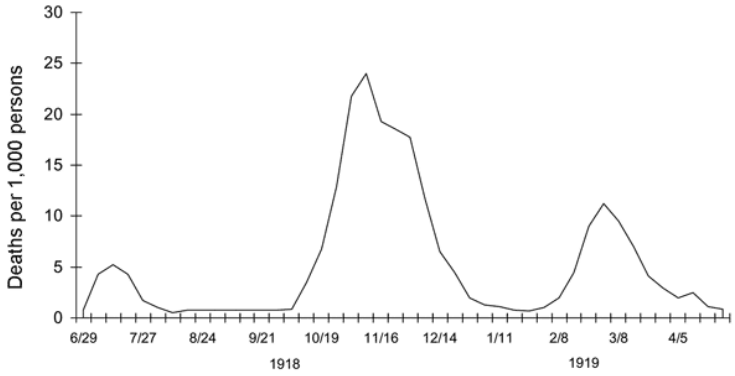

Figure 1. Spanish flu mortality 1918–1919 (from Taubenberger & Morens, 2006).

The symptoms of Spanish flu were exceptionally aggressive. The onset of the symptoms was quick; uninfected people could catch the disease and die before the end of a single day. For many, the disease did not ultimately kill them, but left their bodies susceptible to complications caused by bacteria. The postmortem examinations showed, in many victims, the ultimate cause of death was secondary bacterial infections (such as bacterial pneumonia) in the lungs (Collins, 1931). Spanish flu is thought to have affected up to 40 percent of the world's population. It had a staggering average case fatality rate (CFR) of 1.7 percent deaths per infected individuals (Collins, 1931). It is estimated that 50 to 100 million people worldwide died from the disease or secondary complications incurred because of the disease, which is more than the number of people who died in World War I. In the United States, nearly 675,000 people died (U.S. Department of Health & Human Services, 2014).

In endemic and epidemic influenza, the CFR is typically greater for the older and younger aged populations, due to incompletely developed or atrophied immune systems. This creates a "U" shape in mortality over the age spectrum that can be seen in Figure 2 (see the "December 1921–September 1922" line, which represents the years after the Spanish Flu pandemic). Strangely, the mortality curve for Spanish flu took an unnatural "W" shape. While the older and younger populations remained greatly affected, a relatively high proportion of the 20–40-year-old population also died (Morens & Fauci, 2009). The disease affected an unusually healthy proportion of the population. Experts' opinions differ on why this odd trend actually occurred. Some believe it was due to a

particular immunoprotection gained from the older population, greater than 35, surviving a similar strain (Taubenberger & Morens, 2006). Others believe the unusually high mortality rate among healthy adults was due to an immunological response in these individuals, resulting in enhanced tissue damage (Morens & Fauci, 2009).

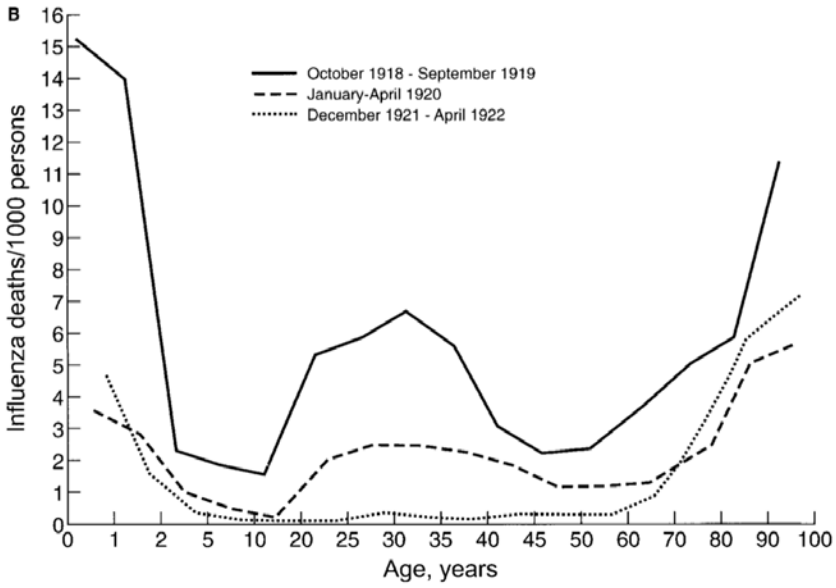

Figure 2. Spanish flu mortality through age spectrum. An unusually high mortality rate existed for healthy adults between 15 and 50 years of age (from Morens & Fauci, 2009).

2. 1928 U.S. Influenza Epidemic

The 1928 epidemic swept through the population of the United States within a decade of the Spanish influenza. It was significantly less severe than Spanish flu due to the limited region of the world it affected; however its case fatality rate was still fairly high. The average case fatality rate was 0.56 percent, roughly one third that of the Spanish Flu CFR (Collins, 1931). The reduced incidence of the epidemic in the United States led to only approximately 100,000 deaths (Bureau of the Census, 1930).

3. Asian Flu (1957–1958)

A new flu virus was identified in February 1957 in the Far East that became known as Asian flu. The United States responded by starting work on a vaccine that would become available in limited supply by August 1957 (Kilbourne, 2006). The disease quietly worked its way into the United States with a series of small outbreaks but spread quickly after children returned to school in the summer of 1957. The infection rates were greatest among school children, young adults and pregnant women (U.S. Department of Health & Human Services, 2014). While the pandemic seemed to be over by December 1957, a second wave of infections continued until March 1958 (U.S. Department of Health & Human Services, 2014).

At the biological level, Asian flu was classified as a H2N2 virus, which was much different than the devastating Spanish flu. Studies have shown that Asian flu evolved from a genetic re-assortment of avian flu, which was different than any influenza virus that had been studied before (Greene & Moline, 2006). This process is referred to as an antigenic shift. The disease is thought to have been a wild duck strain that combined with a previously existing human strain (Greene & Moline, 2006). The world was better prepared for the Avian Flu than it was for the Spanish flu due to advances in medical technology and data collection. Developed countries mobilized to create a vaccine and treat cases to avoid the staggering loss of life that occurred during the Spanish flu.

The Asian flu was overall much milder compared to the Spanish Flu, with a case fatality rate of 0.01 percent for cases under age 49. However, for ages 50–65 and above 65, the CFR climbed to 1.0 and 4.0 percent respectively (Payne & McDonald, 1958). It is estimated that 1–2 million people died from the pandemic worldwide (Rogers, 2013). In the United States, approximately 70,000 people died from Asian flu or complications incurred from Asian flu, with infants and the elderly being the most susceptible to the virus (Rogers, 2013). The effect on the elderly can be seen in Figure 3 by the steady increase in excess mortality rate and premature deaths (death occurring prior to a person's normal life expectancy), starting at age 45 and rapidly increasing at 70 (Dowdle, 1999). The data for infants was not available for this graph.

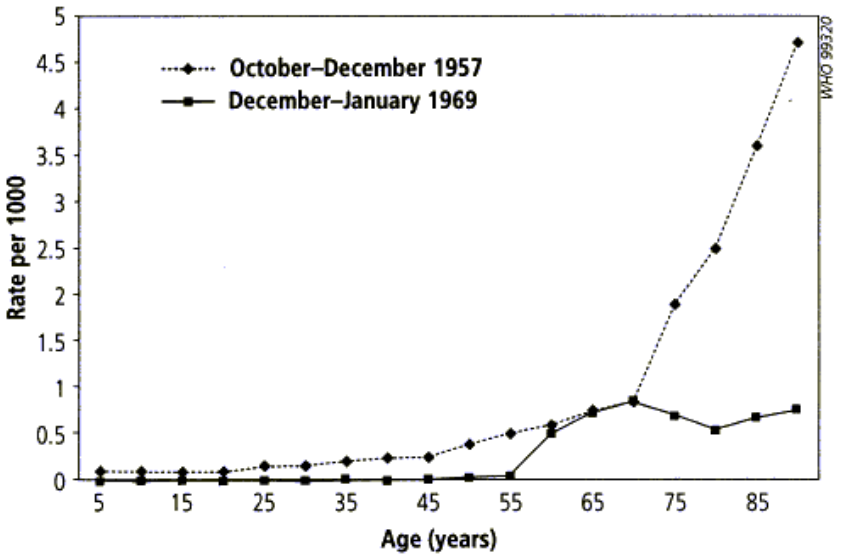

Figure 3. Excess mortality by age for Asian flu (1957) and Hong Kong flu (1969) influenza pandemics (from Dowdle, 1999).

4. Hong Kong Flu (1968–1969)

The influenza strain that caused a worldwide pandemic in 1968 took the name of the place where it was first detected: Hong Kong. The virus made its way to the United States by September 1968 and peaked during the winter. Although the virus returned in 1970 and 1972, it had the lowest death total of all the large pandemics to hit the world in the 20th century (U.S. Department of Health & Human Services, 2014).

The strain was identified as the H3N2, which descended from the Asian flu (H2N2) through an antigenic shift. The estimated average CFR worldwide was less than 0.01 percent for the majority of age groups, climbing to approximately 1.0 percent for cases in people older than 50 (Dowdle, 1999). The strain, mild compared to Spanish flu, is thought to have ultimately led to the death of close to 1 million people (Paul, 2013). It affected people throughout the age spectrum, although the elderly were once again at greater risk. Returning to the graph in Figure 3, it can be seen that people over the age of 65 were most likely to die from the Hong Kong Flu, although the excess mortality increased much less than with the Asian flu (Dowdle, 1999).

5. Swine Flu (2009–2010)

The most recent flu pandemic occurred in 2009. Swine flu, as it became known, was first detected in April 2009. By June, over 18,000 cases had been reported in the United States; by November, a total of 48 states were affected by the pandemic, with the disease most prominent in young people (U.S. Department of Health & Human Services, 2014). The graph in Figure 4 shows the pediatric deaths attributed to the seasonal flu (in green), compared to deaths due to the swine flu pandemic (in pink). The pandemic caused almost three times more pediatric deaths in the United States than the seasonal flu (The Influenza Division of Centers for Disease Control and Prevention, 2010).

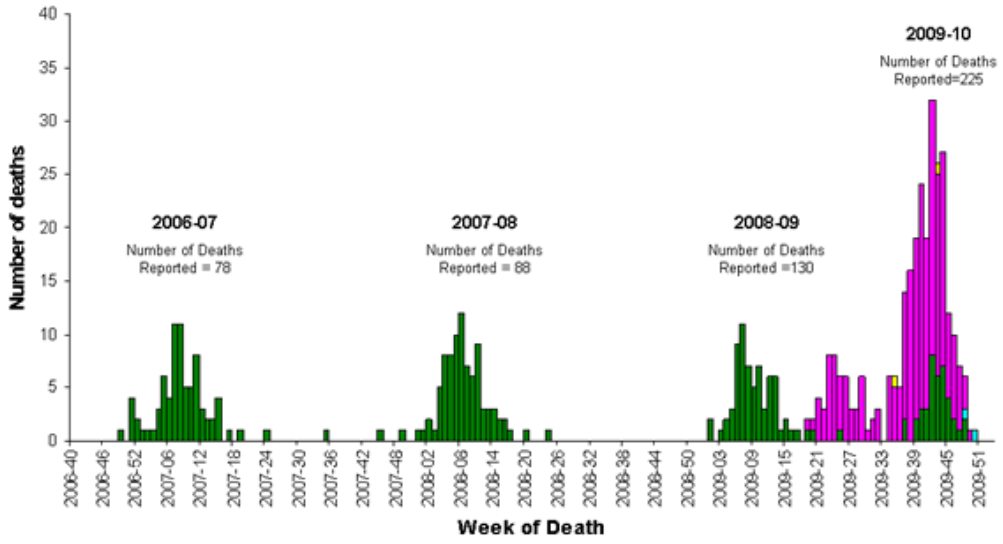

Figure 4. Number of Swine flu associated pediatric deaths by week of death (from The Influenza Division of Centers for Disease Control and Prevention, 2010).

Swine flu had an even greater impact worldwide. The map in Figure 5 shows the locations of deaths from laboratory-confirmed cases of H1N1 throughout the globe. The World Health Organization (WHO) estimates over 18,000 people died from the swine flu (WHO, 2010), although further research has shown that the deaths from the 2009 swine flu pandemic, including secondary complications, may have been over 10 times that number (Simonsen, Spreeuwenberg, & Lustig, 2013). This recent study accounted for the

respiratory deaths precipitating from the flu virus, occurring with higher incidence in older individuals (Simonsen, Spreeuwenberg, & Lustig, 2013). The CFR for the 2009 swine flu was calculated to be 0.007 percent, which is much lower than Hong Kong and Asian flu (Presanis & De Angelis, 2009). Even though the swine flu was relatively mild, it had a significant impact; it swept through the populations of the world despite the best efforts of response agencies with the latest technology.

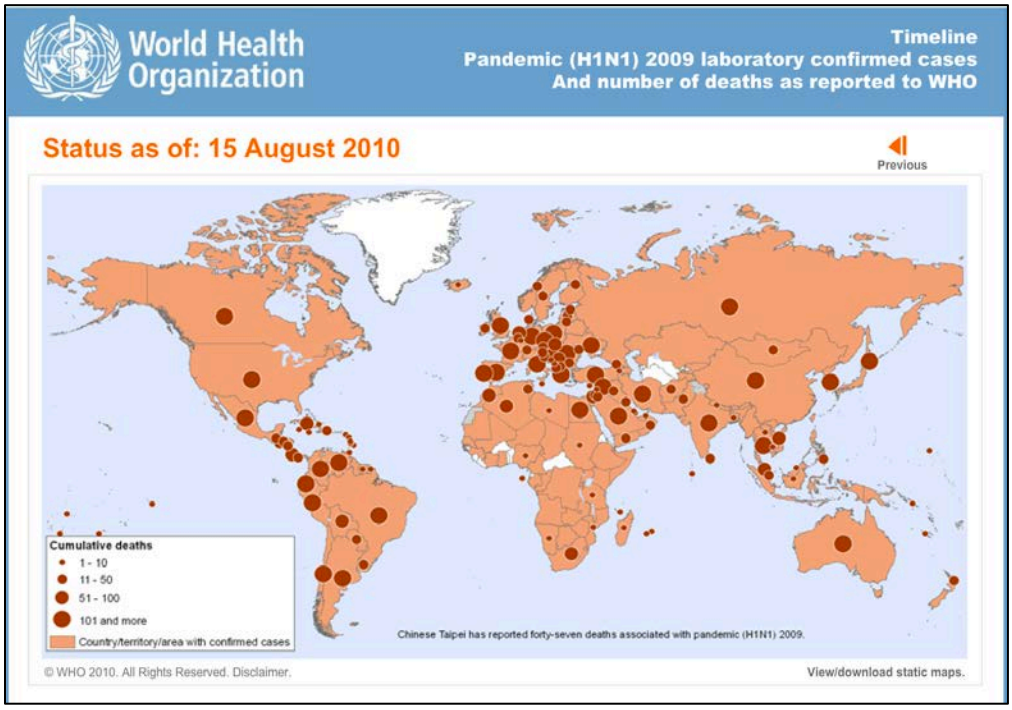

Figure 5. Locations of cases of swine flu by 15, August 2010 (from World Health Organization, 2010).

C. CURRENT PANDEMIC RESPONSE PLAN

The scope of pandemic response plans ranges from large international and national organizations down to the state and local level. The focus of this thesis is on the Texas influenza pandemic response plan; however, it is important to understand the structure of the organizations above the state level. An effective and efficient response to a worldwide pandemic requires planning and cooperation among large international and national institutions, such as WHO, the United States Department of Health and Human

Services (HHS), and the Center for Disease Control and Prevention (CDC), and state and local agencies.

1. International and National Response Plans

WHO sets the International Health Regulations (IHR) and oversees the coordinated effort of many member nations to respond to a multi-national pandemic. HHS is the U.S. government's principle agency for protecting the health of all Americans. A principle component of this agency is the CDC. The CDC is required to protect the public health through, but not limited to, "developing and applying disease prevention and control, environmental health, and health promotion and health education activities" (CDC, 2013, para. 1).

In addition to setting IHRs, WHO periodically updates pandemic preparedness guidance to member states in the form of interim guidance. In 2013, WHO released Pandemic Influence Risk Management. This report highlighted common issues member countries experienced in response to the 2009 Swine flu pandemic. Countries had prepared for a pandemic of high severity but were unable to adapt their national and local plans to a more moderate event (WHO, 2013). Also, the need to communicate clear and concise risk assessments to decision makers emerged as a significant problem (WHO, 2013).

The 2013 interim update created emergency risk management for health (ERMH), which provides member states guidance and technical support in risk management in the following six areas: policies and resource management, planning and coordination, information and knowledge management, health infrastructure and logistics, health and related services, and community ERMH capacities (WHO, 2013). For logistics and infrastructure, WHO manages a strategic global stockpile of antivirals and vaccines, yet, only develops standard operating procedures to rapidly deploy their global stockpile of vaccines (WHO, 2013). In all areas, WHO offers information and guidance instead of regulation. WHO instructs member states to create and update their own pandemic response plans based on local information and circumstances (WHO, 2013).

In the United States, the White House created Homeland Security Presidential Directive 21 in 2007. It directs the department of Homeland Security, charged with ensuring resilience to disasters in the United States, to coordinate with the department of Health and Human Services (HHS) to create a system to enable communities to quickly provide pandemic countermeasures (vaccines, drugs, and therapeutics) to their populations (White House, 2007). This instruction would take a few years before the CDC, which falls under the HHS, revised their standing response plans to adhere to the presidential directive.

Following the Swine flu pandemic, the CDC updated its national pandemic response plan, "Preparedness and Response Framework for Influenza Pandemics." The plan restructures the description of pandemic planning progression to include six intervals across eight domains of preparation. The six intervals are further divided into pre-pandemic intervals and pandemic intervals (Holloway, Rasmussen, Zaza, Cox, & Jernigan, 2014). The pre-pandemic intervals are made up of investigation and recognition. After the onset of an influenza pandemic, the pandemic intervals include initiation, acceleration, deceleration, and preparation (Holloway et al., 2014). Figure 6 shows the progression of pandemic influenza through the CDC intervals.

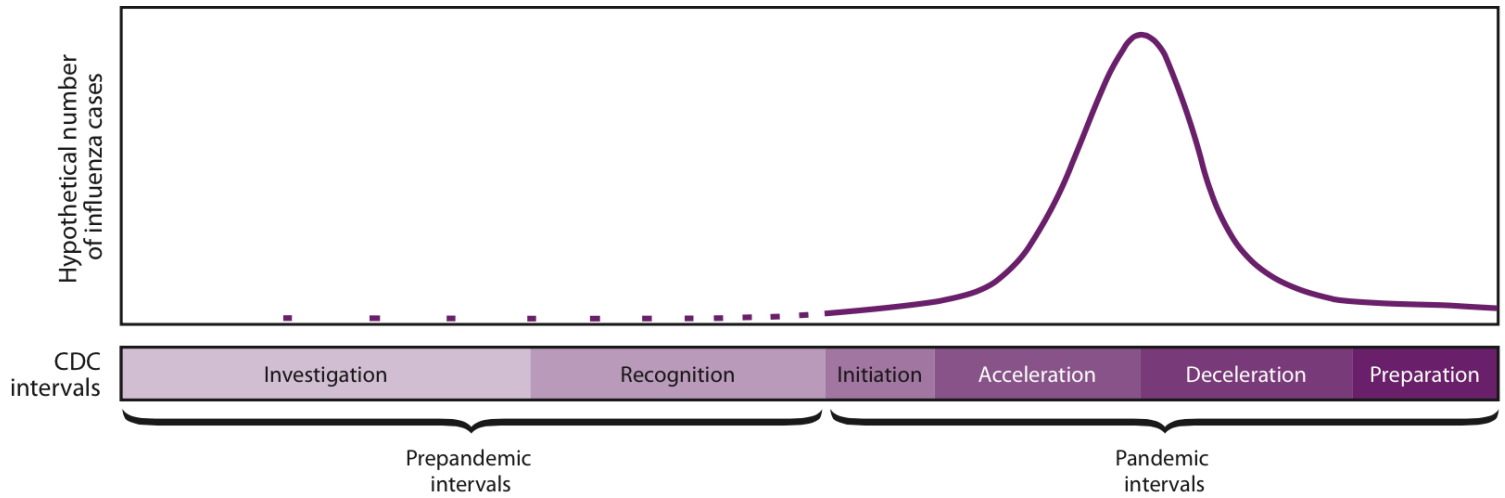

Figure 6. CDC pandemic intervals with hypothetical number of influenza cases, (from Holloway et al., 2014).

The eight domains of preparation delineated by the CDC's plan are incident management, surveillance and epidemiology, laboratory, community mitigation, medial care and countermeasures, vaccine, risk communication, and state/local coordination (Holloway et al., 2014). Of particular note to our discussion are medical care and countermeasures. For each interval the CDC makes recommendations to state and local agencies such as "consider implementation of voluntary quarantine of contacts and chemoprophylaxis of exposed persons based on current recommendations" (Holloway et al., 2014, p. 16) and "monitor antiviral use to identify possible shortages" (Holloway et al., 2014, p. 16). While the CDC recommends benchmarks for each domain across each interval, the foundation of a concrete plan for antivirals is never set. The burden for plans of action, like antiviral distribution plans, is directed to state and local governments.

2. Texas State Response Plan

At the state level, a cohesive pandemic response plan starts to form. The agency tasked with the protection of public health in the state of Texas is the Department of State Health Services (DSHS). They have created a document outlining the Texas pandemic response plan called the Pandemic Influenza Plan Operational Guidelines (PIPOG). The PIPOG adapts guidance from the WHO and CDC to develop a comprehensive strategy to prepare and respond to pandemic influenza in Texas. It outlines three goals: 1) "stopping, slowing, or otherwise limiting the spread of a pandemic into the state," 2) "limiting the spread of a pandemic and mitigating disease, suffering, and death," and 3) "sustaining infrastructure and mitigating impact on the economy and the functions of society." (Texas Department of State Health Services, 2008, p. 7) These guidelines "outline activities and responsibilities for the state, regional, and local public health departments" (Texas Department of State Health Services, 2008, p. 7).

Among the different intervention strategies to accomplish these goals, vaccines are the most effective response, but they require time to develop and then more to produce (Texas Department of State Health Services, 2008). Until the vaccines are a viable option, antivirals coupled with community based mitigation strategies are the primary means of slowing the spread of the pandemic (Texas Department of State Health

Services, 2008). In particular, antivirals will reduce the duration of symptoms of the virus and may prevent certain complications. Antivirals have the added ability to be stockpiled in case of a pandemic so that they can be readily available. Although Texas is in a developed country, antivirals are still considered "limited" in supply if a Spanish-flu-like pandemic were to occur making it paramount to efficiently manage their distribution (Texas Department of State Health Services, 2008). This thesis analyzes the distribution plan for antivirals during an influenza pandemic in Texas. It is important to note, "Antiviral drug countermeasures are one tool of a multi-faceted containment response" (Texas Department of State Health Services, 2008, p. 5).

Planning for the use of antivirals must include "identifying target groups to receive antiviral drugs, allocating and delivering the antiviral drugs, communicating critical information, and monitoring the effects of the drugs in the population" (Texas Department of State Health Services, 2008, p. 5). In 2008, two separate panels of experts at the Texas DSHS created the basis for Texas antiviral allocation. While not mathematically founded, it recommended an adaptive 3-tier priority system to distribute antivirals to target groups: 1) outbreak control, 2) infrastructure, and 3) Risk for complications (Texas Department of State Health Services, 2008). Outbreak control is the primary goal at the onset of pandemic in Texas. Once this goal is accounted for, allocation can proceed to target tiers 2 and 3 (Texas Department of State Health Services, 2008). As a local control state, Texas has created a response plan that is simple and flexible enough to allow decisions to be made on the local level of governance.

The science of developing effective antivirals has progressed quickly in recent times. Currently, the United States has three licensed antiviral agents: peramivir (Rapivab), zanamivir (Relenza), and oseltamivir (Tamiflu). This paper will focus on primarily two of these, zanamivir (Relenza) and oseltamivir (Tamiflu), which are from a class known as neuraminidase inhibitors (NI) that prevents a virus from reproducing (CDC, 2015). NIs have been proven to have a significant reduction in the duration and severity of flu symptoms if an infected person receives the antivirals within the first 48 hours after becoming symptomatic (CDC, 2015).

The origin of Texas's antiviral drug stockpile comes from three distinct supplies: DHSH cache, Texas General Revenue (GR) cache, and the Texas allotment from the Strategic National Stockpile (SNS) (Texas Department of State Health Services, 2008). The first two stockpiles are maintained by the state of Texas but the SNS is only released by the CDC to the state of Texas when WHO declares a worldwide influenza pandemic. While the current number of SNS antivirals is classified, the number of antivirals allocated as of 2007 was approximately 4 million, with the possibility to buy more at a subsidized price (Texas Department of State Health Services, 2008). The DSHS cache, a small cache of slightly over 100,000, will be the first used if it is determined that a pandemic is imminent. It will initially be divided evenly between eight DSHS Health Service Regions (HSR) and the DSHS Austin office for preemptive distribution to first responders (Texas Department of State Health Services, 2008).

After the pandemic is declared, the antiviral drugs from the DSHS GR cache and SNS, the bulk of the antivirals available, will be distributed based on targeting certain population groups in order to minimize morbidity and mortality, minimize economic effects, and minimize social disruption (Texas Department of State Health Services, 2008). Figure 7 represents the current Texas antiviral allocation guidance. This plan relies on vigilant surveillance and analysis of influenza-like illness (ILI) patterns in the population. Distribution decisions will be made using the "latest science," which includes the array of large-scale mathematical models contracted through local universities and private groups, and "input from participants in two Expert Panels convened by DSHS" (Texas Department of State Health Services, 2008).

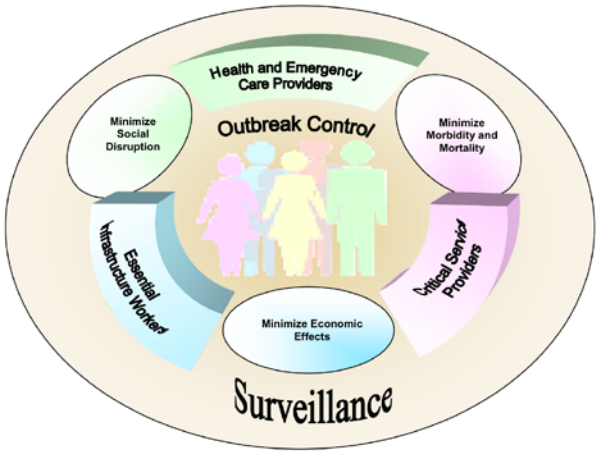

Figure 7. Texas DSHS antiviral release guidance (from Texas Department of State Health Services, 2008).

D. MOTIVATION AND OUTLINE

The Texas DSHS antiviral distribution in response to pandemic influenza is adaptable and flexible, however it does not provide a concrete release plan. They instruct panels of experts to make allocation decisions using current mathematical models, but these models are not specified. This thesis is part of a project team that has been tasked to create a revised mathematical model. The optimization model from this thesis has been implemented in an online tool to aid decision makers distribute antivirals in the state of Texas.

Texas carries unique characteristics that challenge the prevention and response to a statewide pandemic. Texas's population characteristics such as size, population densities, and the availability of health care services, as well as geography create a considerable problem for responding to an influenza pandemic. Texas is larger, geographically, than the 14 smallest states in the United States combined (Texas Department of State Health Services, 2008). Out of the 254 counties in Texas, 116 (46%) are considered primary care health professional shortage areas, 64 (25%) have no hospital, 178 (70%) qualify as fully medically underserved areas, and 46 (18%) as partially medically underserved areas (Texas Department of State Health Services, 2008). In addition, Texas shares 1,250 miles of border with Mexico and has two international

airports that rank in the top ten for passenger counts in the country (Texas Department of State Health Services, 2008). There are six seaports including two that serve the cruise ship industry. In the state of Texas it is estimated that without intervention a pandemic similar to the 1918 Spanish Flu could infect 7 million Texans and result in 1.4 million deaths (Texas Department of State Health Services, 2008).

The unique challenges of preparing and responding to a statewide pandemic require the use of precision tools that use the most cutting-edge understanding of the problem. The goal of this paper will be to improve the current mathematical model used to guide the release of antivirals in the state of Texas. Chapter II includes an in depth literature review of disease spread models and intervention optimization. Chapter III defines the specific objectives of this paper's model. Also, it explains the model itself to include sets, data, formulation, variables, objective function, constraints, and assumptions. Chapter IV reports the analysis of several scenarios as well as a comparison to the analysis of a similar model, the Texas pandemic flu simulator. Finally, Chapter V will draw the conclusions from this model and recommend follow-on research.

II. LITERATURE REVIEW

Developing mathematical models to predict and respond to infectious disease epidemics is a rapidly emerging field of study. Modern computer-aided analytical techniques have opened up a previously underdeveloped area in the study of epidemiology. Analytical methods are developed to model the spread of a disease through a population as well as optimizing intervention strategies. It is important to effectively manage and coordinate advances in pandemic response, such as vaccines, antivirals, and social interventions, to significantly reduce the spread and severity of an infectious disease.

As covered in the previous chapter, Texas DSHS policy directs the "panel of experts" to determine the best antiviral distribution throughout the state of Texas utilizing the "latest science." Under this policy, the Texas DSHS has sponsored several mathematical models to aid in the antiviral allocation, distribution, and storage. Located on the "Texas Pandemic Flu Toolkit" website (at http://flu.tacc.utexas.edu), the models can be accessed and used by the decision makers. The toolkit incorporates a powerful age-risk structure disease spread simulation model called the "Texas Pandemic Flu Simulator." Accompanying the disease-spread model are three intervention optimization models, two of which we will not focus on in this paper: the Texas Vaccine Allocation model and the Texas Ventilator Stockpiling model. The Texas Antiviral Distribution model, the interventional model of focus, optimizes the distribution of antivirals in the state of Texas using a facility-location optimization model. It is this intervention optimization model that this paper will seek to replace with an improved model using data from the Texas Pandemic Flu Simulator.

A. DISEASE SPREAD MODELS

Differential equations (DE) are one of the oldest and most consistently used disease-spread models. In 1927, Kermack and McKendrick first developed a deterministic differential equation epidemiological model with the susceptible population density exceeding the critical value resulting in an epidemic. Decades later Rvachev

(1968) created the first spatial and temporal model using DEs to represent the spread of influenza through the USSR. Hethcote conducted a comprehensive review of the progression of disease-spread models in 2000. In it he describes that, since the middle of the 20th century, DE models have improved significantly and are now use in tandem with modern computing techniques to more accurately model the spread of a disease (Hethcote, 2000).

In DE models, often referred to as compartmental models, a population is divided into several homogeneous subgroups, or compartments, that are mutually exclusive (at one given time if a temporal dimension exists). Each member of a compartment is assumed to have the exact same epidemiological state. The simplest compartmental differential equation model is the SIR model. Susceptible (S), Infected (I), and Recovered (R) population groups are represented by three mutually exclusive compartments. The rate of change of these groups can be seen in the equations from Hethcote in Figure 8. Given a population of size N, the susceptible compartment can become infected with a rate proportional to the contact rate, Beta, and the size of the susceptible and infected populations. The Infected group recovers with the rate gamma and transitions the recovered group (from Hethcote, 2000).

$$
\begin{aligned}
dS/dt &= -\beta IS/N, & S(0) &= S_o \geq 0, \\
dI/dt &= \beta IS/N - \gamma I, & I(0) &= I_o \geq 0, \\
dR/dt &= \gamma I, & R(0) &= R_o \geq 0,
\end{aligned}
$$

Figure 8. Susceptible, Infected, and Recovered (SIR) compartmental model equations (from Hethcote, 2000).

A DE compartmental model can range from very simple to extremely complicated. The number of compartments determines the granularity. Granularity is the extent to which a model is broken down into parts. A course-grain model is not extensively broken down, resulting in an undetailed but simple model. A fine-grained model is broken down extensively providing a significantly complicated model. Also, a

deterministic model can evolve into a stochastic model by adding probabilistic parameters to the differential equations, therefore complicating the model even more.

A more complicated compartmental model than SIR is the MSEIR model. M and E are compartments inserted for births with temporary passive immunity and exposed, but not yet infectious, respectively. As the acronym hints at, individuals in the temporary passive immunity group (M) can move to Susceptible, which can move to Exposed, which can move to Infected, which can then move to Recovered. Deaths can occur in any of the compartments. The flow chart from Figure 9 illustrates the dynamics of the MSEIR model (Hethcote, 2000).

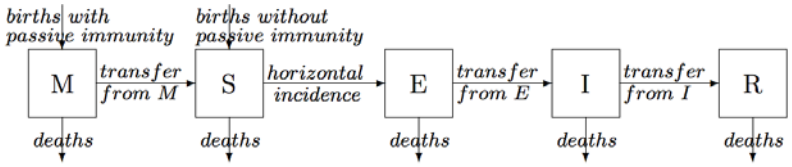

Figure 9. General transfer diagram for passive immunity MSEIR model with, susceptible, exposed, infected, and recovered classes (from Hethcote, 2000).

The use of mitigation strategies can increase the number of compartments and therefore the granularity of the model. Colburn, Wagner, and Blower (2009) divide the mitigation strategies into two distinct types: behavioral public health interventions and biomedical. Quarantine and isolation measures are examples of behavioral interventions. The left-side flow chart from Figure 10 adapts a compartment model to account for quarantine. Susceptible, Exposed, and Infected groups have their individual quarantined states represented by Q_S, Q_E, and Q_I respectively (Coburn et al., 2009). Only the Q_S may return to its original group once it determines to not have been infected. The use of biomedical intervention methods is shown on the right-side flow chart in Figure 10. Vaccinated individuals move to V, in which they are immune to the disease (Coburn et al., 2009). Once an individual is infected, he or she moves to the group T if they have been treated with antivirals.

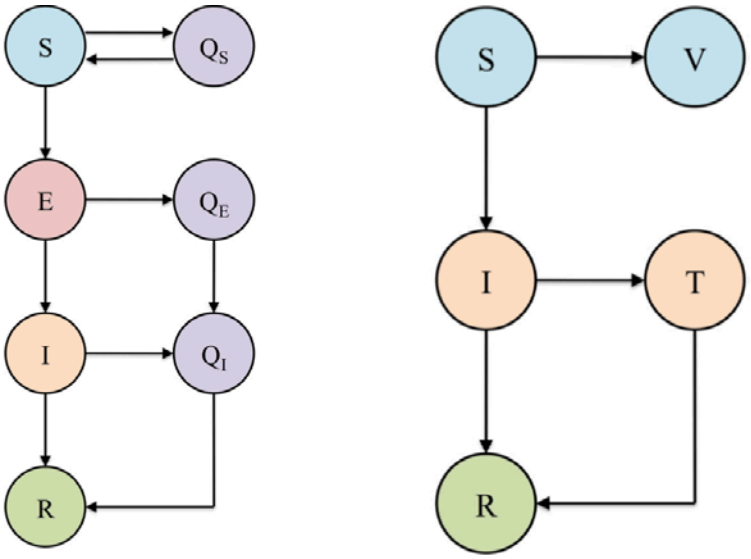

Figure 10. General transfer diagrams for SEIR model with quarantine compartments (Q_S, Q_E, Q_I) and SIR model with vaccination and antivirals (V and T respectively) (from Coburn et al., 2009).

The SIR model can be extended to a geographically large regional model with heterogeneous population density to show both spatial and temporal movement of an influenza epidemic. In a recent model, Cahill, Crandall, Rude, and Sullivan (2005) create a space-time model combining mass action, in which a large number of people simultaneously behave in a similar manner, with lattice and stochastic principles. They divide the United States into 10^6 land patches, cells, of 10 km^2, in which an independent compartmental SIR model occurs in each (Cahill et al., 2005). They allow interactions to occur between neighboring cells in the geographic lattice. For example, a susceptible compartment has a location and time component, denoted as $S_{(x,y,t)}$. Stochastic interactions are included in some of the parameters such as contact rate. Finally, demographic age classes are included with population groups of infant (0.5–5 years), child (5–18 years), middle (18–65), and old (65–infinity) to create even greater granularity of the heterogeneous population (Cahill et al., 2005). This model provides much detail about the propagation of a disease through the United States.

Finally, the Texas Pandemic Flu Simulator model, created by Medlock, Meyers and Galvani, (2009) improves the temporal-spatial model further. The Texas Department of State Health Services (DSHS) has adopted this model to use in epidemic decision-

making. It uses a modified SEIR model incorporating two separate SEIR categories, one for an unvaccinated and one for a vaccinated group. A flow chart depicting the model is shown in Figure 11. The heterogeneous model also has 17 age bins (0, 1–4, 5–9, 10–14…70–74, 74+), which are then further divided into low-risk and high-risk (Medlock et al., 2009). High-risk people are defined as those with an existing condition such as asthma or pregnancy (Medlock et al., 2009).

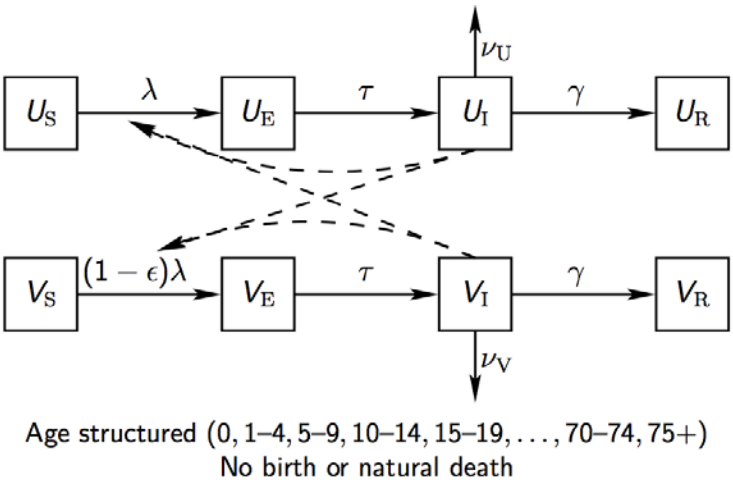

Figure 11. Texas Pandemic Flu Simulator transfer model for unvaccinated (U_S, U_E, U_I, U_R) and the vaccinated (V_S, V_E, V_I, V_R) SEIR compartments, (from Medlock et al., 2009).

The Medlock et al. (2009) model also connects many compartmental models through a network structure in which each node is a county in Texas connected to other nodes through stochastic movement. At each of the nodes a separate compartmental model simulates the progression of pandemic influenza with a modified SEIR. The SEIR compartments are divided into unvaccinated (U_S, U_E, U_I, U_R) and the vaccinated (V_S, V_E, V_I, V_R) (Medlock et al., 2009). The movement in the model assumes that infected individuals will travel for work only during the latent period, which is prior to the onset of symptoms, and only travel to seek health care after the onset of symptoms.

The model includes three forms of intervention: vaccination, social distancing, and antivirals (Medlock et al., 2009). The social distancing is disseminated through public announcements encouraging hygienic precautions, health care seeking guidelines,

and social distancing recommendations. The mode calculates valuable epidemic quantities like total state treatable cases, hospitalizations, deaths by age/risk group, and timing and magnitude of epidemic peak. The data was used to analyze several release schedules of vaccines (Medlock et al., 2009). We will be incorporating the results from this disease-spread model to target a specific population group with an antiviral release schedule.

B. INTERVENTION OPTIMIZATION MODELS

While predictive models of infectious disease propagation have evolved greatly, true optimization of intervention strategies is far more limited. This is due in part to the complexity of the predictive models; Intervention strategies such as antivirals, vaccinations and social distancing can be incorporated into the disease spread models, but the optimization of these strategies to a specific demographic, location, or time is extremely complicated.

Most examinations of intervention strategies have utilized adjustments to the compartmental models discussed in the previous section. Khazeni, Hutton, Garber, Hupert, & Owens (2009) use the compartmental epidemic model combined with a Markov model of human disease transmission of the first wave of 2009 Influenza A (H1N1) to examine the effects of nonpharmaceutical interventions, including closing school and child care facilities, home isolation, cough etiquette, hand washing, use of personal protective equipment, and vaccinations. They used measures of effectiveness (MOE) that include infections and deaths, quality-adjusted life-years (QALYs), and incremental cost effectiveness ratios (Khazeni et al., 2009). QALYs accounts for the expected remaining lifespan of the deceased individual to weigh lives with more remaining lifetime greater. The study found that earlier vaccination against pandemic H1N1 2009 prevents more deaths, increases QALYs, and is more cost saving that other vaccination schedules (Khazeni et al., 2009).

Our model uses results from a compartmental disease spread model that uses similar stochastic human transmission on a larger scale, on the state level instead of a generic U.S. city. Also, we optimize the release schedule of an antiviral intervention with

a linear program instead of examining the effects of interventions with sensitivity analysis on different scenarios. Although our model investigates the use of nonpharmaceutical intervention strategies and vaccines, it uses very similar measures of effectiveness to the measures of effectiveness use: mortality rates and QALYs to determine.

With limited vaccine and antivirals capabilities around the world, the development of a precision release schedule for medical countermeasures become paramount. Matrajt and Longini (2010) created a compartmental epidemic model to investigate vaccine intervention. Their model examines sensitivity analysis by varying the timing and composition of vaccine release schedules on developed counties (DC) and less developed countries (LDC) populations with moderately severe strains of H1N1 influenza. The results show that an earlier release schedule of vaccines, before the peak vice after, drastically reduces the number of influenza infections, therefore reducing the total number of influenza deaths and hospitalizations (Matrajt & Longini, 2010). Demographically, the targeting of high and low risk children starting on day 20 of an epidemic greatly reduces the prevalence compared to targeting high-risk children and adults on day 20 (Matrajt & Longini, 2010).

The model used by Matrajt and Longini uses a similar compartmental epidemic model to the one used by the Texas Pandemic Flu Simulator. Once again this model only conducts sensitivity analysis on a simulated progression of H1N1 Influenza through a human population; however the results highlight the importance of an early release schedule using death rates and hospitalizations, which are similar to the MOEs that we use in our model. Also, the results of the model emphasize the importance of targeting certain demographic groups with regards to age and risk. Our model seeks to use antiviral optimization to target demographic groups to reduce similar MOEs in the state of Texas.

The release of vaccines depends on the timing of their development after the emergence of a pandemic influenza strain. Until that happens, the best intervention strategies, antivirals and social distancing measures, must be implemented to provide the greatest benefit the population. Logini, Halloran, Nizan, and Yang (2004) used a compartmental stochastic epidemic simulation to evaluate the effectiveness of targeted

antiviral's administered prophylactically, treating the actual disease and not just symptoms, to respond to an avian strain of influenza. The model used discrete-time progression of the pandemic through a community of 2,000 people with a typical demographic cross-section (Longini et al., 2004). The antiviral allocation targeted identified influenza cases and their immediate contact mixing groups such as households, day-care centers, playgrounds, and schools. They found that the epidemic would be contained if 80% of these exposed persons maintained prophylaxis for up to 8 weeks (Longini, et al., 2004). The model predicts a reduction in the illness attack rate, which is the speed of progression of the disease in numbers of new cases per population, of 2% (Longini et al., 2004). Also, the model predicted a reduction in death rate of 0.04 deaths per 1,000 persons. This improvement is comparable to vaccinating 80% of the population (Longini Jr., Halloran, Nizam, & Yang, 2004).

The scale of Logini et al.'s (2004) model focused on a single "typical" American community of individuals afflicted with an Asian-influenza strain. Our model will scale up to the state level, specifically Texas, to examine many strains of pandemic influenza. Once again, the authors used a stochastic compartmental model to evaluate the impact of an intervention strategy. Their model demonstrates that antivirals can be used effectively, by targeting, to contain a pandemic and lower the death rate, however, their method did not find a truly "optimal" antiviral allocation strategy. We determine the optimal release schedule with a mixed integer linear program (MIP).

Although many variations of stochastic compartmental models have been coupled with sensitivity analysis on targeted intervention strategies to lower the morbidity and mortality of a pandemic, we found limited studies that used optimization to determine the minimum morbidity or mortality achievable through those strategies. These problems are very complicated due to non-linearity and stochasticity of the models. Patel, Longini, and Halloran (2005) use genetic algorithms (GA) and random mutation hill climbing (RMHC) algorithms to find near optimal vaccine distributions by minimizing the overall illness in the population and lives lost. Both GA and RMHC randomly vary combinations of decision variables to search for a near optimal solution to a non-linear optimization program.

They found the GA and RMHC produced an optimal vaccine distribution that was 84% more effective than random mass vaccination in the mid-range of the vaccine availability (Patel et al., 2005). While we do not intend to use a GA or RMHC, the ability of an optimization program to develop a clearly superior vaccine distribution has been demonstrated through this study. We avoid a non-linear problem by using the results from a compartmental model to solve a stochastic linear program that produces the optimal antiviral distribution.

More recently, Dimitrov, Goll, Hupert, Pourbohloul, and Meyers (2011) optimized the distribution of SNS antivirals in the United States with a large-scale optimization program. They combined a nationwide network model for inter-city travel throughout the United States with a compartmental model for intra-city disease progression to create a hybrid H1N1 transmission model (Dimitrov et al., 2011). They implement policy decisions on many stochastic simulations of pandemic influenza using this model. In order to optimize such a large set of time-based intervention policies, they utilize a creative optimization algorithm called upper confidence bounds applied to trees (UCT) that allows a multi armed bandit algorithm to avoid searching each branch of the tree and still find the optimal set of policies (Dimitrov et al., 2011). Eleven possible policy decisions where examined each month over a twelve month period: 0, 1, 5, 10, 25, or 50 million courses distributed proportional to population or prevalence (Dimitrov et al., 2011). They found that the optimal allocation of antivirals policy either matches or significantly outperforms the other policies, especially in response to extremely severe strains of influenza (Dimitrov et al., 2011).

The Dimitrov et al. (2011) model approaches a very similar problem to what we will focus on in this thesis: the demographic, spatial, and temporal optimization of antivirals. This model differs from our model in that the scale of Texas does not demand such a complicated model. While our model seeks to determine a higher granularity by creating a very specific release schedule, it will not run along with the stochastic simulation. Rather, it takes in the results from many stochastic simulations to determine the optimal antiviral release schedule through the state of Texas. In doing this, we require a simple stochastic linear program instead of an intricate network search algorithm.

The Texas DSHS tasked Singh, Huang, Morton, Galvini, and Meyers (2013) through the University of Texas to create an antiviral optimization model to distribute antivirals geographically in the state of Texas. Their optimization model maximizes the access of targeted populations, either the entire population of Texas or the underinsured population, to antivirals throughout the state (Singh et al., 2013). The granularity of the model divides Texas into its 1939 ZIP code tabulation areas (ZCTAs). Their model uses a willingness-to-travel model to predict how far each ZCTA will travel for antivirals, but did not incorporate any variety of epidemic spread model (Singh et al., 2013). The model would not provide the infected population access to antivirals, but simply the target populations.

The willingness-to-travel model used National Household Travel Survey (NHTS) data from 2009 to estimate the fraction of the target population that would travel to obtain antivirals (Singh et al., 2013). They assumed that the NHTS data could apply to similar travel trends in the state of Texas. Also, while the survey did not cover a willingness to travel to obtain medical care directly, they used social travel, such as a privately operated vehicle (POV) for travel to work, school, family, and social reasons, as a proxy, which likely underestimates the willingness to travel.

Singh et al. (2013) used a type of mixed integer linear program (MIP) that is commonly referred to as a facility-location model. The program maximized the access of the target population by determining the optimal ZCTAs to distribute antivirals in the state of Texas (Singh et al., 2013). The ZCTAs would in turn distribute to the pharmacies to provide a point of pickup for the antivirals. The program was then run with GAMS using CPLEX. The optimization model was used to compare the tradeoff between the Texas population served antivirals and number of ZCTAs receiving antivirals for a target population of the entire population of Texas. As the number of people served increases, the marginal benefit decreases (Singh et al., 2013). The graph from Figure 12 shows the diminishing return in population served as the number of ZCTAs increases.

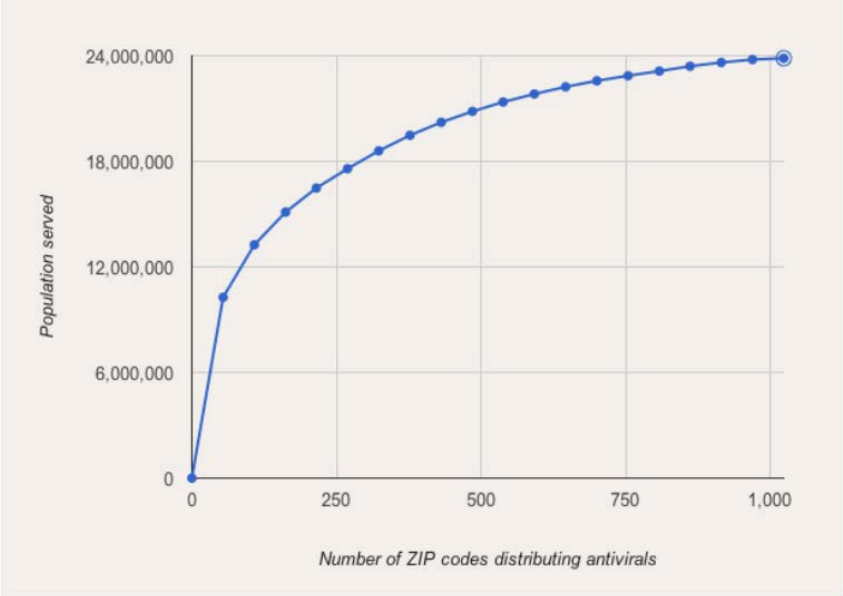

Figure 12. Efficiency tradeoff between expected population receiving antivirals and the total number of ZCTAs selected after optimized for entire population (from Singh et al., 2013).

The Singh et al. (2013) optimization model is included in the Texas Pandemic Flu toolkit as the "Texas Antiviral Distribution." We have created a *new* model that improves the distribution of antivirals. We add a time dimension to the antiviral distribution creating a temporal-spatial antiviral release schedule. We use the spatial-temporal results from the Texas Pandemic Flu Simulator, the Texas DSHS disease spread model, to optimize the release of antivirals to target the treatable population of Texas, the critical division of the infected compartment that has been symptomatic for less than 48 hours. We tailor the antiviral release schedule to recent influenza pandemics incorporating randomness into the disease parameters. Also, we expand the age-demographic granularity of the state of Texas to 20 categories, rather than just entire population and underinsured population.

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III. MODEL

A. OBJECTIVES

We formulate an optimization model for use in an online tool to aid decision makers in the distribution of antivirals in the state of Texas. The Texas DSHS sponsored our project and currently uses it as a resource for pandemic response in Texas. Texas Antiviral Release Scheduling (TAVRS) is available to users online through an easy to use interface. Appendix A provides a tutorial on how a decision maker uses TAVRS to create an antiviral release schedule. It shows how the user can customize the antiviral distribution by selecting inputs such as strain type(s), pandemic geographic origin, current cases statewide, and optimization criteria. TAVRS then uses our model to optimize the antiviral release schedule. The output from our model is then displayed in TAVRS so that it can be easily interpreted and understood by the decision makers.

We use IBM ILOG CPLEX (CPLEX, 2015) to solve our mixed integer linear program in the General Algebraic Modeling System, or GAMS (GAMS, 2015). My formulation uses the following sets: counties, time, and population group, which is a set of 20 age-demographic categories. The decision variables in the optimization program are the numbers of antivirals released to each county in each time period. The program optimizes the benefit of the antivirals that are picked up in each set. We use the number of sick individuals in the population that respond best to antivirals, known as the treatable population, to determine who seeks to pick up antivirals in each set. The user chooses one of three benefits to optimize: lives saved, hospitalizations avoided, or QALYs. The output from the model is number of antivirals released to each county at each time.

We incorporate our optimization model into TAVRS to aid decision makers to answer the following:

- Which counties in Texas should the Texas DSHS release antivirals to achieve the most benefit to the population of Texas?
- When should Texas DSHS release antivirals?

- How can the antiviral release schedule target the sick population that responds best to antivirals?
- How should the antiviral release schedule account for differences in societal and age demographic benefits?

Taking these objectives into account, we first describe the sets and data of the optimization model in sections B and C respectively before presenting the mathematical formulation in section D, and then concluding with model assumptions in section E.

B. SETS

Time is the first set used in the model. This set is adjustable; it can be divided into small time periods, such as days. Using longer time periods produces a coarser model, but it is more practical operationally and computationally. The decision makers at Texas DSHS make decisions on the order of weekly, bi-monthly, or monthly rather than daily. Designing an adjustable time set ranging from weekly to monthly matches the requirements of the decision makers to the design of the program.

The next set used in the optimization model is the counties. Texas is the second largest state in the United States and is comprised of 256 counties, seen in Figure 13. The largest counties are on the western side of the state, the largest of which is Brewster County with an area of 6,193 square miles. At the other end of the spectrum, the smallest counties are on the eastern portion of the state. The smallest county is Rockwall County, near Dallas, and is a miniscule 129 square miles in size. Populations of the counties also vary greatly. Texas has five major population centers: Houston, Dallas, Fort Worth, San Antonio, and Austin. The counties associated with these cities are very large. The most populated county in Texas is Harris County, which includes Houston with just over 4 million people living in it. Harris County contains twice as many as the next most populated county. The least populated county in Texas is Loving County, near the border with New Mexico, with a population of just 82 people. The disparity in size and population of counties in Texas makes distribution of antivirals an interesting problem.

The counties in Texas are identified according to their Federal Information Processing Code (FIPS) number. The state of Texas has the state FIPS code of 48. The

counties in Texas begin with Anderson County that has a FIPS code of 1, followed by Andrews at 3. The number increases with odd numbers sequentially through all Texas counties, ordered alphabetically.

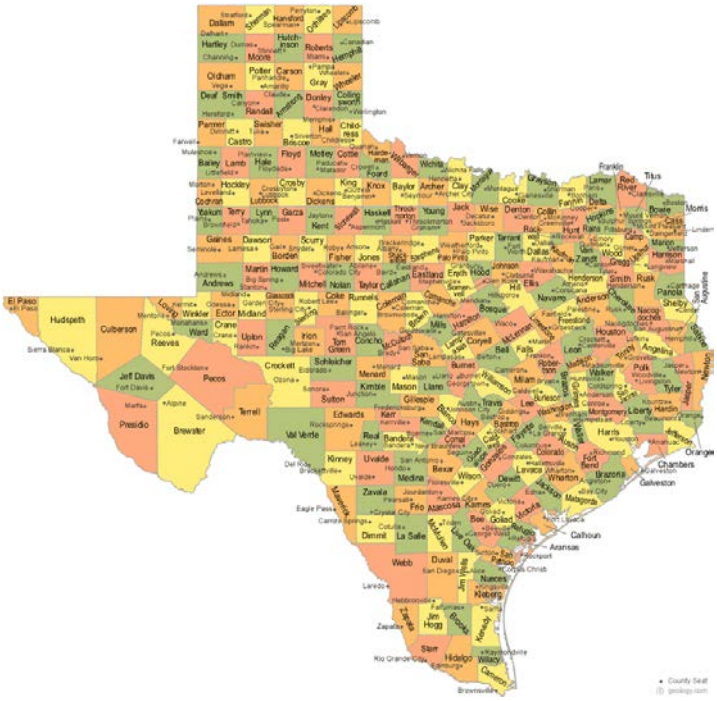

Figure 13. The counties in Texas (from Geology.com, 2015).

The final set of the optimization model is population groups, which corresponds to 20 mutually exclusive and exhaustive age-demographic categories. We base these sets on the work of Meyers, Medlock, and Galvani (2009). Their age-structured SEIR model divided the population into 17 age groups (0, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and 75+) based on 2007 census data. These 17 groups were combined into 5 age groups (0-4, 5–17, 18–44, 45–64, 65+) for larger granularity and easier interpretation.

Each age group is broken down further into four demographic groups: high-risk for influenza complications (high-risk), low-risk for influenza complications (low-risk), first responders, and pregnant. In the epidemiological sense, high-risk is defined as having a chronic condition such as asthma, chronic bronchitis, emphysema, coronary

heart disease, angina, heart attack, diabetes, stroke, weak kidney, epilepsy, cerebral palsy, movement disorders, and muscular dystrophies (Medlock et al., 2009). Also, immune system compromised conditions, such as cancer in the past 3 years, HIV/AIDS, dialysis, and organ transplant, are included in the high-risk category as well (Medlock et al., 2009). Table 1 shows the proportion of each age group that is high risk. While the age groups in the Table do not line up with the model's age groups, it is assumed that the people are distributed uniformly in each age group.

Also, the population of each county has a percentage of worried-well. The worried-well represent the portion of the population that has influenza like symptoms yet does not in fact have the disease. They unnecessarily admit themselves to local hospitals and remove valuable intervention resources from pharmacies (Doshi, 2009). The worried-well are modeled as 0.07 percent of the population.

Table 1. Proportion of high-risk population (from Medlock, Meyers, & Galvani, 2009).

Ages	Proportion High Risk, P_{Ha}
$<$ 6 m	1.51%
6 m–1	4.22%
1–4	8.86%
5–18	11.92%
19–24	18.79%
25–49	20.15%
50–64	33.83%
65+	53.15%

C. DATA

Major data inputs into the antiviral release schedule optimization model are the time, location, and population group of treatable sick people, the benefit from these people picking up antivirals, and the locations and times that the antiviral courses become available to be released. It is important to note here that this tool is available only to Texas DSHS decision makers. The availability of antivirals is not disseminated to the public.

1. Treatable Population Data Input

The treatable population is the first input into the antiviral optimization program. In this section we define treatable population data, investigate its source, and discuss its structure. Then we investigate how to add randomness into the input by taking the expected value of many influenza scenario runs.

a. The Treatable Population

The antiviral release schedule targets the sick population in Texas that will respond best to antivirals, known as the treatable population. The data is not empirical; it comes from the results of an influenza spread simulation using the Texas Pandemic Flu Simulator (TPFS), discussed in Chapter 2. According to this simulation, as a disease spreads the population of Texas will progress from the susceptible compartment, to the exposed compartment, to the infected compartment (Sick), and finally either recover or become deceased. The treatable population is a subgroup of the infected population compartment that has been symptomatic for less than 48 hours. TPFS tracks the number of treatable individuals in each set during a simulation run. The individuals in this brief window will have the greatest impact from using antivirals.

The TPFS requires several different parameters to simulate the spread of influenza pandemic through the population of Texas. These parameters can be divided in three types: disease parameters, origin of initial cases, and intervention allocation and parameters. Intervention allocation includes ventilator distribution, antiviral release schedule, and vaccine allocation. Along with each intervention allocation is intervention parameters. We did not use any intervention allocations in our disease-spread simulation, however the antiviral release schedule and associated parameters will be used later in the analysis. The disease parameters along with their definitions are as follows:

- *Basic Reproduction Number, R_0:* is the number of new cases one case creates on average throughout the course of its infectious period in an uninfected population.
- *Latency Period (Days):* average latency period of the influenza strain.

- *Asymptomatic Period (Days):* the average asymptomatic infectious period.
- *Infectious Period (Days):* is the average total infectious period.
- *Case Fatality Rate:* denotes the fraction of infected individuals that will die as a result of infection, divided by age groups.

The location, timing, and population group of treatable individuals will vary between two simulation runs with identical disease and geographic origin parameters. This is because the TPFS incorporates randomness into the movement of individuals geographically as well as movement of individuals between compartments through the course of the pandemic. An average of multiple simulation runs with identical parameters will provide a more accurate picture of how treatable people will change throughout the course of a pandemic.

Figure 14 shows an example of how the treatable population changes as an influenza pandemic spreads through Texas, known as treatable curves. It shows the average number of treatable people from selected counties over 150 simulations for a mild strain of influenza with the same border geographic origin propagating through the 5–24 high-risk population. The number of treatable people in El Paso County peaks approximately 50 days prior to when Travis County, where Austin is located, peaks. Travis County, in turn, peaks a little more than 50 days before Dallum County peaks. El Paso is located in the extreme western part of Texas, while Austin is located in the very center and Dallam is located in the rural panhandle. As can be seen, the timing, location, and number of treatable people will vary greatly throughout the course of an influenza pandemic

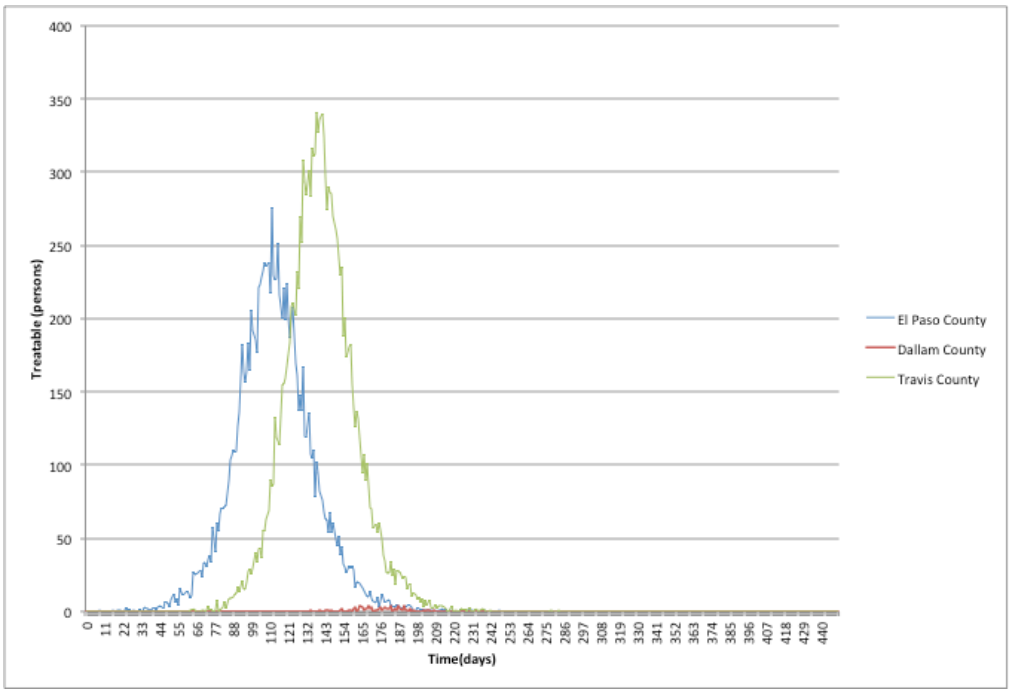

Figure 14. Expected treatable people 5–24 high-risk group for selected counties.

b. Library of Scenarios: Varying Pandemic Parameters

TAVRS must be able to model antiviral release schedules for different influenza scenarios. Each influenza scenario involves a unique influenza strain originating in certain geographic region. A library of treatable curves is incorporated into TAVRS to give decision makers the ability to model different pandemic scenarios that could occur in Texas. TAVRS averages the treatable curves for the scenario or scenarios that a decision maker wishes to model in order to be used in our optimization model.

The TAVRS library of scenarios consists of 2,250 individual treatable curves created through the TPFS by varying five different strains of influenza with three geographic origin regions resulting in 15 influenza scenarios of 150 simulation runs each. Within each influenza scenario of 150 runs, similar disease and geographic origin parameters were chosen but held constant. Disease and geographic origin parameters were varied from among a similar set to incorporate additional randomness into an already stochastic disease spread model.

Two disease parameters, basic reproduction rate (R_0) and CFR, were manipulated to simulate the five strain types (2009-like, 1968-like, 1957-like, 1928-like, and 1918-like). For each influenza strain type, the case fatality rates remained constant for each applicable age group. The R_0 for each strain was randomly selected between the upper and lower bounds for each simulation run. The rows of Table 2 show the five epidemic strains that were included in the TAVRS library along with the parameter values of each.

Table 2. CFRs and R_0 selection for strain simulations (from Meyers & Dimitrov, 2014).

	case fatality rate					reproduction number	
Epidemic Type	***0-4 yrs***	***5-24 yrs***	***25-49 yrs***	***50-65 yrs***	***65+***	***R_0 lower bound***	***R_0 upper bound***
2009-like	0.000092	0.000168	0.000343	0.000253	0.000037	1.4	1.55
1968-like	0.000096	0.000134	0.0002215	0.0013765	0.0100185	1.55	1.75
1957-like	0.0001	0.0001	0.0001	0.0025	0.02	1.55	1.75
1928-like	0.0087	0.0011	0.003	0.0098	0.0403	1.75	2.3
1918-like	0.0196	0.0156	0.016	0.0068	0.0151	1.75	2.3

While the CFR was held constant for each run within a scenario and the R_0 was varied within its associated range for each scenario, the remainder of the influenza disease parameters stayed constant throughout all the runs in all the scenarios. Table 3 shows the values of the remaining disease parameters.

Table 3. Disease parameters for creation of treatable data.

Disease	
Basic Reproduction Number	Variable
Latency Period (Days)	1.2
Asymptomatic Period (Days)	1.9
Infectious Period (Days)	4.1
Case Fatality Rates	Variable

The three geographic origin regions were created by varying the number and location of counties and the number of initial cases in each of those counties. The locations for the three geographic origin regions are determined by randomly selecting a uniform number of counties between 1 and 10 from all counties in Texas (Random), from all counties after being weighted by population size (Population), and from Mexico border counties weighted by migration rates (Border). Within each county selected, the number of initial cases was randomly selected from a uniform distribution of 1 to 20 cases. Table 4 shows the variations of the each geographic origin region.

Table 4. Geographic origin region parameters (from Meyers & Dimitrov, 2014).

Geographic Region	# counties chosen	Location criteria	# initial cases
Random (G1)	U~(1,10)	Random from all counties	U~(1,20)
Random Weighted (G2)	U~(1,10)	Random from all counties, weighted by population size	U~(1,20)
Migration Weighted (G3)	U~(1,10)	Random from Mexico border counties, weighted by migration rates	U~(1,20)

Our optimization model uses the average number of treatable individuals for each time in each county for each population group. For example, if the decision maker wishes to create an antiviral release schedule for a 1918-like Spanish influenza that originated

from Texas-Mexico border counties, TAVRS would average the 150 treatable curves that apply to that influenza scenario to be used in our optimization model. If the decision maker wishes to create an antiviral release schedule for an influenza that could be similar to a 1957-like or a 1968-like that originated from the population centers in Texas, TAVRS would average the 300 treatable curves that apply to those influenza scenarios to be used in our optimization model.

2. Antiviral Benefit

We next consider the benefit that the antivirals provide for the target population. We examine three separate objectives in the model to provide the decision makers with the flexibility to target certain benefits. The three benefits are maximizing lives saved, hospitalizations avoided, and Quality Adjusted Life Years (QALYs). We derive the benefit of minimizing deaths and hospitalizations using odds ratios and relative ratios, respectively. The subsequent calculation of QALYs is an extension of the lives saved which incorporates the remaining life expectancy of the age group of the life saved.

a. Lives Saved

The lives saved benefit is defined as the number of lives saved when the treatable population picks up antivirals. This benefit is calculated by using two values: the mortality odds ratio and the case fatality rates. The case fatality rates are the same strain specific rates from the disease spread model inputs (see Table 2). They are the rate at which the infected population will die due to the disease or complications from the disease. The mortality odds ratio is the odds that an infected person will die given antiviral treatment compared to dying without antivirals. More specifically, this is the measure of the odds of an exposed group (antivirals) experiencing a certain outcome (death) against the opposite outcome (survived) compared to the odds of an unexposed group (no antivirals) with that same ratio. In this odds ratio, both the unexposed and exposed groups are infected with influenza. Equation 1 explains the mortality odds ratio mathematically.

$$MortOR = \frac{\left(\frac{\#\text{ exposed to AVs and Died}}{\#\text{ exposed to AVs and survived}}\right)}{\left(\frac{\#\text{ not exposed to AVs and Died}}{\#\text{ not exposed to AVs and survived}}\right)} \quad (1)$$

If the odds ratio is approximately equal to one, then antivirals have no effect on the odds of death. If the odds ratio is less than one then antivirals will decrease the odds of death. The mortality odds ratio information comes from a metadata study on close to 30,000 patients during the 2009 Swine flu pandemic (Muthuri, et al., 2014). Table 5 summarizes the mortality odds ratio for each age demographic group. Administering antivirals to pregnant women between 25 and 49 years of age carries a significantly better improvement in mortality rate (odds ratio is 0.46) compared to high-risk individuals between the ages of 5 and 24 with an odds ratio of 0.82.

Table 5. Mortality odds ratios.

Description	MortOR
0-4 years low risk	0.82
0-4 years high risk	0.82
5-24 years low risk	0.82
5-24 years high risk	0.82
5-24 years first responder	0.81
5-24 years pregnant women	0.46
25-49 years low risk	0.75
25-49 years high risk	0.75
25-49 years first responder	0.75
25-49 years pregnant women	0.46
50-64 years low risk	0.75
50-64 years high risk	0.75
50-64 years first responder	0.75
65+ years low risk	0.75
65+ years high risk	0.75

The lives saved benefit is found by subtracting the probability an infected person dies from influenza after *receiving antivirals* from the probability an infected person dies from influenza *without antivirals*. The probability an infected person dies from influenza *without antivirals* is known as the case fatality rate (see Table 2), which is dependent on

strain type and age group. After substituting CFR and Probability of death after receiving antivirals into the definition of odds ratio (Equation 1), straightforward algebra yields:

$$P\{Death \mid AVs\} = \frac{\frac{CFR(MortOR)}{1-CFR}}{\left(1+\frac{CFR(MortOR)}{1-CFR}\right)} \tag{2}$$

Hence, the decrease in probability of death follows:

$$P\{LivesSaved \mid AVs\} = \mathrm{CFR} - P\{Death \mid AVs\} = \mathrm{CFR} - \frac{\frac{CFR(MortOR)}{1-CFR}}{\left(1+\frac{CFR(MortOR)}{1-CFR}\right)} \tag{3}$$

Using this calculation, the age-demographic specific lives saved benefits were calculated. The lives saved benefits for 2009-like Swine flu and 1918-like Spanish flu, in units of lives saved per antiviral, are displayed in Table 6. The lives saved benefits for Spanish flu are much higher than Swine flu representing a potential for much greater life savings when the treatable population uses antivirals during a severe strain. The potential for saving lives during a mild strain, where not many people die, is much less. There is a negative benefit for the worried-well at the bottom of the table. This value represents the potential benefit lost because a possible antiviral is not available for infected person. We determined this to be the negative value of the average benefit to the total population of Texas.

Table 6. 2009-like swine flu and 1918-like Spanish flu lives-saved benefit.

	2009-like Swine Flu	1918-like Spanish Flu
0-4 years low risk	0.0000166	0.0034711
0-4 years high risk	0.0000166	0.0034711
5-24 years low risk	0.0000302	0.0027720
5-24 years high risk	0.0000302	0.0027720
5-24 years first responder	0.0000319	0.0029264
5-24 years pregnant women	0.0000907	0.0083630
25-49 years low risk	0.0000857	0.0039518
25-49 years high risk	0.0000857	0.0039518
25-49 years first responder	0.0000857	0.0039518
25-49 years pregnant women	0.0001852	0.0085759
50-64 years low risk	0.0000632	0.0016913
50-64 years high risk	0.0000632	0.0016913
50-64 years first responder	0.0000632	0.0016913
65+ years low risk	0.0000092	0.0037321
65+ years high risk	0.0000092	0.0037321
Worried Well	-0.0000578	-0.0037830

b. Hospitalizations Avoided

The hospitalizations avoided benefit is defined as the improvement in the probability of a person becoming hospitalized when administered antivirals. When this benefit is applied to the number of people receiving antivirals in Texas, the result is a total number of hospitalizations avoided. This benefit is calculated using hospitalization rates and hospitalization relative risk, a slightly different comparison ratio than odds ratio. Hospitalization rates are the age-demographic rates that the infected population will be hospitalized due to the disease. Hospitalization rates are in units of hospitalizations per 100,000 person years.

Hospitalization relative risks are the relative risk a person infected with influenza will become hospitalized after using antivirals compared to without using antivirals. More specifically, this is the measure of the risk of an exposed group (antivirals) experiencing a certain outcome (hospitalized) against all the people in the exposure group (antivirals) compared to the risk of an unexposed group (no antivirals) with that same ratio. In this relative risk of hospitalizations, both the unexposed and exposed groups are infected with influenza. Equation 4 explains the hospitalization relative risk mathematically.

$$HospRR = \frac{\left(\frac{\#\text{ exposed to AVs and Hospitalized}}{Total\ \#\text{ exposed to AVs}}\right)}{\left(\frac{\#\text{ not exposed to AVs and Hospitalized}}{Total\ \#\text{ not exposed to AVs}}\right)} \quad (4)$$

Table 7 shows the hospitalization rates and hospitalization relative risks for each age-demographic group. The hospitalization rates are based on (Thompson, et al., 2004). The Hospitalization relative risks are based on (Dutkowski, 2010), (Lee, et al., 2007), and (Siston, et al., 2010)).

Table 7. Hospitalization rates and hospitalization relative risk.

Description	HospRate	HospRR
0-4 years low risk	26.3	0.5
0-4 years high risk	26.3	0.49
5-24 years low risk	11.5	0.71
5-24 years high risk	11.5	0.7
5-24 years first responder	11.5	0.71
5-24 years pregnant women	11.5	0.81
25-49 years low risk	11.5	0.71
25-49 years high risk	11.5	0.7
25-49 years first responder	11.5	0.71
25-49 years pregnant women	11.5	0.81
50-64 years low risk	53.3	0.71
50-64 years high risk	53.3	0.7
50-64 years first responder	53.3	0.71
65+ years low risk	259.8	0.63
65+ years high risk	259.8	0.63

The hospitalizations avoided benefit is found by subtracting the probability of an infected person becoming hospitalized due to influenza after *given antivirals* from the probability of an infected person becoming hospitalized due to influenza *without being given antivirals*. The probability an infected person becomes hospitalized from influenza *without antivirals* is known as the hospitalization rate (Table 7), which is dependent on population group. After substituting hospitalization rate and Probability of hospitalization after receiving antivirals into the definition of relative risk (Equation 5), simple algebra yields:

$$P\{Hospitalization \mid AVs\} = HospRR(HospRate) \quad (5)$$

Therefore, the decrease in probability of hospitalization follows:

$$P\{HospitalizationsAvoided \mid AVs\} = HospRate - HospRR(HospRate) \quad (6)$$

Using this equation, the age-demographic specific hospitalizations avoided were calculated. The hospitalizations avoided benefits, in units of lives saved per antiviral per 100,000 people, are displayed in Table 8. This metric, unlike lives saved, does not depend on flu strain and, therefore, remains constant for all strains. Once again, the worried-well have an impact. They detract from the hospitalizations avoided benefit with the negative value of the average hospitalizations avoided from all populations groups.

Table 8. Hospitalizations avoided benefit.

Description	Hospitalizations Avoided (per 100,000 people)
0-4 years low risk	13.15
0-4 years high risk	13.41
5-24 years low risk	3.34
5-24 years high risk	3.45
5-24 years first responder	3.34
5-24 years pregnant women	2.19
25-49 years low risk	3.34
25-49 years high risk	3.45
25-49 years first responder	3.34
25-49 years pregnant women	2.19
50-64 years low risk	15.46
50-64 years high risk	15.99
50-64 years first responder	15.46
65+ years low risk	96.13
65+ years high risk	96.13
Worried Well	-19.36

c. QALYs

The quality adjusted life years benefit is a variation off of the lives saved benefit. The basic premise is that a younger life saved is worth more than an older life saved because they are expected to have more years left before they die. This is done through the expected lifetime for each age group, calculated by using (United States Social Security Administration, 2009). The QALYs benefits for 2009-like Swine flu and 1918-like Spanish Flue, in units of expected quality adjusted life years saved per antiviral, are displayed in Table 9. The worried-well are included in the QALYs antiviral benefit table as well. They take the value of the negative benefit of the average QALY benefit over all population groups.

Table 9. 2009-like swine flu and 1918-like Spanish flu QALYs benefit.

	2009-like Swine Flu	1918-like Spanish Flu
0-4 years low risk	0.0013136	0.2753691
0-4 years high risk	0.0013136	0.2753691
5-24 years low risk	0.0020277	0.1859000
5-24 years high risk	0.0020277	0.1859000
5-24 years first responder	0.0021404	0.1962585
5-24 years pregnant women	0.0060836	0.5608586
25-49 years low risk	0.0038788	0.1788003
25-49 years high risk	0.0038788	0.1788003
25-49 years first responder	0.0038788	0.1788003
25-49 years pregnant women	0.0083790	0.3880163
50-64 years low risk	0.0017046	0.0455911
50-64 years high risk	0.0017046	0.0455911
50-64 years first responder	0.0017046	0.0455911
65+ years low risk	0.0000607	0.0244771
65+ years high risk	0.0000607	0.0244771
Worried Well	-0.0017500	-0.1145660

3. Antiviral Availability

The third data input into the optimization program is the time-phased number of antivirals available. The courses of antivirals available are a combination of the Texas DSHS cache, the General Reserve cache, and the release of the Texas allotment from the Strategic National Stockpile. This availability is adjustable based on the user inputs. For example, initially Texas may have 100,000 antiviral courses stored and ready to use. They may expect to receive 2,000,000 antiviral courses one month after the onset of the pandemic and an additional 2,000,000 courses two months after.

D. FORMULATION

Indices

$t \in T$ set of time increments (adjustable days, weeks, bi-weeks, months) T={T1,T2,…}

$c \in C$ set of all counties in Texas (FIPS code) C={1,3… 507}

$p \in P$ set of all mutually exclusive population groups (age/risk group) P= {"0-4 years high risk,"" 25–49 years pregnant women"…}

Data

$pop_{c,p,t}$ expected number of people seeking antivirals in county *c*, in population group *p*, at time *t*

ben_p expected benefit of a person in population group *p* receiving antivirals [lives saved, hospitalizations avoided, QALYs saved]

$avail_t$ additional antivirals courses available for distribution at time *t* [integer]

$M = \sum_{t \in T} avail_t$ large constant equal to the total number of antivirals available during the entire planning period [integer]

Decision Variables

$R_{c,t}$ number of antivirals released in county *c* at the start of time *t* [courses]

$P_{c,p,t}$ number of people picking up antivirals in county *c*, population group *p*, in time *t* [expected number of people]

$S_{c,t}$ number of antivirals available on the shelf in a county *c* at time *t* [expected courses]

$F_{c,t}$ fraction of the demand for antivirals satisfied in county *c* in time *t*; [0-1]

$X_{c,t}$ equal to 0 if all the demand for antivirals in county *c* in time *t* is satisfied and 1 otherwise; [binary]

Formulation

$$Maximize \sum_{c,p,t} P_{c,p,t} * ben_p \tag{7}$$

Subject to:

$$\sum_{t' \in T: t' \le t, c \in C} R_{c,t'} \le \sum_{t' \in T: t' \le t} avail_{t'} \qquad \forall t \in T \tag{8}$$

$$S_{c,0} = R_{c,0} \qquad \forall c \in C \tag{9}$$

$$S_{c,t} = R_{c,t} + S_{c,t-1} - \sum_{p \in P} P_{c,p,t-1} \qquad \forall c \in C, t \in T, t > 0 \tag{10}$$

$$\sum_{p \in P} P_{c,p,t} \leq S_{c,t} \qquad \forall c \in C, t \in T \tag{11}$$

$$P_{c,p,t} \leq pop_{c,p,t} \qquad \forall c \in C, t \in T, p \in P \tag{12}$$

$$(\sum_{p \in P} pop_{c,p,t}) - S_{c,t} \leq X_{c,t} \bullet \sum_{p \in P} pop_{c,p,t} \qquad \forall c \in C, t \in T \tag{13}$$

$$P_{c,p,t} = (F_{c,t}) \bullet pop_{c,p,t} \qquad \forall c \in C, t \in T, p \in P \tag{14}$$

$$F_{c,t} \geq \frac{S_{c,t}}{\sum_{p \in P} pop_{c,p,t}} - M \bullet (1 - X_{c,t}) \qquad \forall c \in C, t \in T \tag{15}$$

$$F_{c,t} \geq 1 - X_{c,t} \qquad \forall c \in C, t \in T \tag{16}$$

$$X_{c,t} \in \{0,1\} \qquad \forall c \in C, t \in T \tag{17}$$

$$R_{c,t}, P_{c,p,t}, S_{c,t}, F_{c,t} \geq 0 \qquad \forall c \in C, t \in T, p \in P \tag{18}$$

E. EXPLANATION OF FORMULATION

The optimization formulation is broken down into three parts: decision variables, the objective function, and the constraints.

1. Decision Variables

The decision variables in the optimization program are made up of three positive real variables, a fraction between 0 and 1, and a binary variable. The positive variables, $R_{c,t}$, $P_{c,p,t}$, $S_{c,t}$, govern the number of courses of antivirals released, the number of courses of antivirals that are picked up, and the number of antivirals remaining on the shelf, respectively. The fraction $F_{c,t}$ and a binary variable $X_{c,t}$ are also important variables to determine who picks up antivirals if a shortage of antivirals exists. The large constant M is used to set the fraction of each population that can pick up antivirals if an antiviral shortage exists.

The solution to the integer linear program provides the optimal number of courses of antivirals to release to county c at the beginning of time frame t. This is ultimately the number that is most important number to the decision maker to create the antiviral release schedule. The formulation represents the ability of the state to distribute courses of antivirals to counties, which then in turn distribute to pharmacies. The antivirals will be

on a first come first serve basis as it is released to the pharmacies. Unless an extreme situation exists during the course of a pandemic, Texas DSHS is unable to instruct the pharmacies to only provide antivirals to a particular demographic age group.

The value of $P_{c,p,t}$ is the number of antiviral courses that are picked up by population group p, during time frame t, in county c. The value of $P_{c,p,t}$ depends on whether the entire treatable population of that county is satisfied with antivirals and the composition of age-demographic groups in a county. If the expected total treatable people, the "demand" for antivirals, in a particular county c and timeframe t are not satisfied by the number of antivirals on the shelf a shortage exists. In this case, the model assumes that the each age-demographic group will pick up the antiviral courses off the shelf with the same proportion. If the "demand" for antivirals is satisfied, there is no shortage and therefore no restriction on which population group picks up antivirals because everyone that wants antivirals can get them.

The decision variable $S_{c,t}$ denotes the number of antivirals on a shelf in county c during time frame t. The fraction $F_{c,t}$ sets the fraction of each population group that picks up antivirals in an antiviral shortage situation. Finally, the binary variable $X_{c,t}$ denotes when a shortage exists by taking the value of 1 if the demand, the treatable people, are not satisfied, and a 0 otherwise.

2. Objective function

The objective function will maximize the expected total benefit of all the antivirals picked up. Equation (7) sums the benefit for each population group picking up a course of antiviral multiplied by the number of people in that population age group picking up a course of antiviral over each population group p, each county c, and each time frame t. Maximizing this value in the objective function will maximize the number of lives saved, number of hospitalization avoided, or the expected number of life years saved.

3. Constraints

The first constraint prevents the formulation from releasing more antivirals than are actually available. For every time *t*, equation (8) sums the number of antivirals released on or before time *t* to each county *c* on the left side. This value is set to remain less than or equal to the number of courses of antivirals that are available on or before time t'. Constraint set (9) sets the number of antivirals on the shelf in the initial time frame to equal to the number of antivirals released in the initial time frame for each county. This constraint can be adjusted later to account for alternate initial conditions.

Equation (10) accounts for the carry-over of unused antivirals from one time frame to the next. For every county *c* and time *t* that comes after the initial time frame, the number of antivirals on the shelf is equal to the number of antivirals released during that time frame plus the number of antivirals on the shelf the time frame prior minus the number of antivirals picked up by all the populations groups during the time frame prior.

Equation (11) prevents more antivirals than are on the shelf from being picked up. The equations sets the number of antivirals picked up by all the population groups to be less than or equal to the number of antivirals on the shelf at time *t* in county *c*. Equation (12) prevents more antivirals from being picked up than there is demand. For every county *c*, population group *p*, and time frame *t*, the number of antivirals picked up must be less than or equal to the number of people seeking antivirals.

The next three equations govern how the antivirals are picked up if a shortage exists, that is if the total demand for antivirals is greater than the number of antivirals on the shelf. Conversely, if all the treatable people can be satisfied, a shortage does not exist. Equation (13) sets the shortage binary variable, $X_{c,t}$, if a shortage exists. If the demand for antivirals is not satisfied in time period *t* and county *c*, then the variable $X_{c,t}$ is set to 1. Also, if a shortage exists, equation (14) ensures that the same fraction of individuals receives antivirals in each population group for time frame *t* and county *c*. This prevents any discrimination between population groups picking up antivirals.

Equation (15) sets the shortage variable, $X_{c,t}$, to zero if the demand cannot be met. Setting the shortage variable to zero subtracts the large *M* from the right side, relaxing the

fraction of the population satisfied. Finally, Equation (16) ensures that all the demand is satisfied if no shortage exists.

The final two equations (17) and (18) define the range of values for the decision variables. The binary variable $X_{c,t}$ is set to take on either 1 or 0 in equation (17). $R_{c,t}$, $P_{c,p,t}$, $S_{c,t}$, and $F_{c,t}$ are all set to be continuous variables greater than or equal than 0 with equation (18). Specifically, we create the release variable, $R_{c,t}$, as a continuous variable for efficiency. This will produce fractional releases of antivirals. In reality the antivirals are released in batches, however, it is unlikely that modeling $R_{c,t}$ as an interger or as batches would change the release guidance output from the model.

F. ASSUMPTIONS MADE ABOUT THE MODEL

The optimization model requires certain assumptions to be made. First, the model assumes that the pickup of antivirals by the treatable population will not affect the transmission of the influenza pandemic and therefore have no effect on the progression of the disease through the population. This allows the model to be run with the results of the disease spread simulation model and not simultaneously.

The next assumption involves the worried-well population. The worried-well is the population that has not contracted the influenza virus but is seeking antivirals. They may have flu like symptoms or just be extremely worried. The optimization model assumes that the if the worried-well population picks up antivirals, then it will have a negative effect on the benefit. This negative benefit, instead of zero benefit, represents the taking of an antiviral from a person that needs it.

Also, the model assumes that antivirals picked up by each member of a population group will have the same effect. The model assumes that all of the treatable population will seek antivirals. Finally, the model assumes that each population group will pick up the same fraction of antivirals if a shortage exists.

IV. RESULTS AND ANALYSIS

The Texas Antiviral Release Scheduler, with our antiviral optimization model, is currently available to the Texas DSHS as an online tool in the Texas Pandemic Flu Toolkit through the following link: http://flu.tacc.utexas.edu/scheduling/. A walk-through example of how to create an antiviral release schedule with TAVRS can be found in Appendix A, although access is required to use the online tool.

TAVRS quickly provides decision makers at the Texas DSHS optimal antiviral release schedules using the current and expected conditions of the influenza pandemic in Texas. Using a weekly antiviral release schedule, a typical GAMS (GAMS, 2015) model has approximately 750,000 variables, including 16,000 binary variables, and slightly over 400,000 constraints. The CPLEX (CPLEX, 2015) solver generally finds the optimal solution in less than 15 seconds on a 2012 MacBook pro using OS X Yosemite 10.10.2 emulating Windows 8.1, however for a 2009-like border scenario it takes approximately two minutes and 32 seconds.

Although many variations of antiviral release schedules can be created using TAVRS, the following chapter initially examines the worst-case scenario: A 1918-like, Spanish, influenza spreading through the population of Texas. We then vary the parameters to examine how the results change. The variations include variations of the geographic origin the pandemic, variation of the strain to a 2009-like influenza, variations of the total number of antivirals available, and variations of the objective that TAVRS optimizes. Following this sensitivity analysis, we compare the lives saved using TAVRS to the calculated lives saved using the Texas Pandemic Exercise Tool, a downloadable version of the Texas Pandemic Flu Simulator disease spread model for use on a personal computer.

A. 1918-LIKE INFLUENZA PANDEMIC

The base case considers a 1918-like influenza pandemic that begins in a random county in the state of Texas and maximizes the number of lives saved. We assume 30 million antivirals are available immediately at the onset of the pandemic. This number of

antivirals ensures that each person in Texas could have access to them, although this number is much larger than will be needed. The base case scenario represents the best response available to a worse case influenza strain.

Figure 15 shows the number of antivirals released to the entire state at each time period throughout the course of the pandemic. It also includes the number of expected cases treated, which correlates to the number of antivirals picked up by the treatable population, the P decision variable from the optimization formulation. The courses wasted are the number of antivirals that picked up by the worried-well population. Finally, the last trend line displays the number of treatable people that do not have access to antivirals due to the release schedule. Not shown in the figure is the optimal number of lives saved; TAVRS maximizes the number of lives saved to be 26,552 lives.

The graph from Figure 15 shows that the antivirals are not all released immediately. The largest single distribution, approximately four million antivirals, is released at week seven, which is just prior to the largest rise in treatable cases of influenza. The leading edge of the treatable cases begins to rise during the fifth week and peaks during the 11th week at close to 1.7 million cases. The antiviral release schedule continues to distribute antivirals in two more bulk releases during weeks nine and eleven, but not as large as the week seven release. After week 12, the antivirals begin to be distributed in smaller and smaller releases, ultimately finishing after week 27. The courses wasted stays constant at roughly 200,000 courses from week five through week 23, the majority of the pandemic.

The base case represents an unrealistic situation with 30 million antivirals available, but this situation may illustrate a weakness of the model. Due to the scale of the chart in Figure 15 the infected without antivirals appears to be zero, but actually climbs to 20,000 and 5,000 at the beginning and end of the pandemic respectively. The treatable population is not released enough antivirals to satisfy the demand when the number of worried-well is greater in counties at the beginning and end of the pandemic, even though there is an extreme surplus of antivirals available. The curves from Figure 16 show the total number of antivirals released is slightly greater than 14 million, much less that the 30 million available.

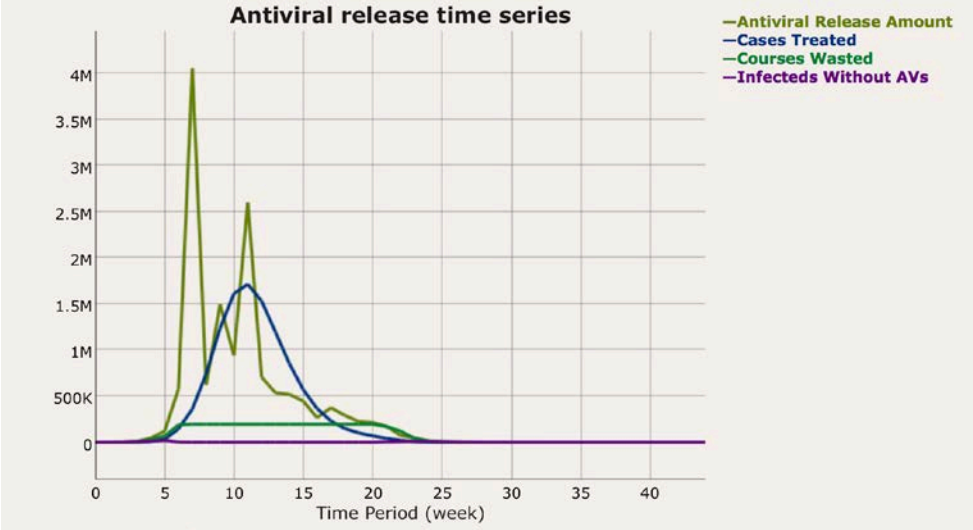

Figure 15. Time phased statewide antiviral release schedule in response to a 1918-like random-origin influenza pandemic with unlimited antivirals maximizing lives saved (after Texas Antiviral Release Scheduling, 2015).

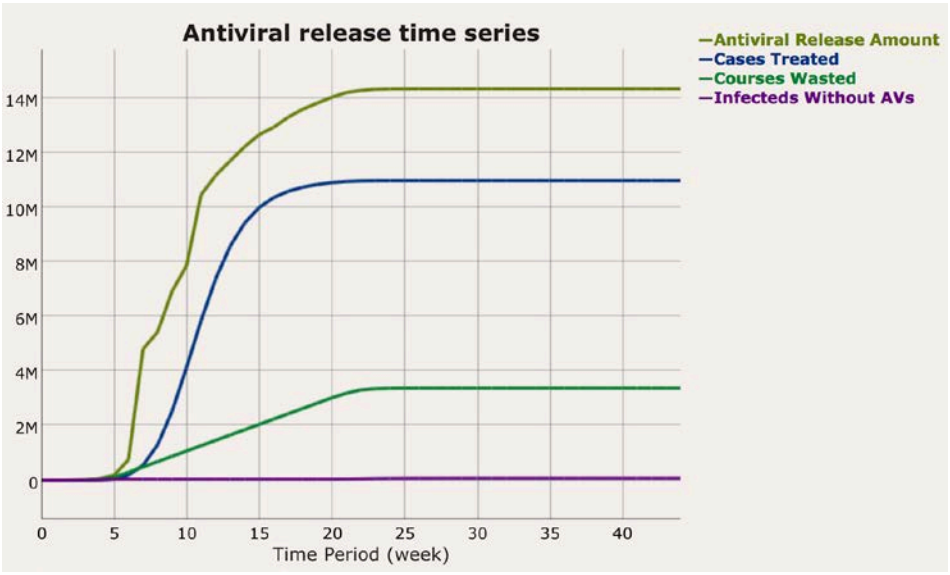

Figure 16. Time phased cumulative statewide antiviral release schedule in response to a 1918-like random-origin influenza pandemic with unlimited antivirals maximizing lives saved (after TAVRS, 2015).

Snapshots from the antiviral release schedule are displayed geographically in response to the base case pandemic in Figure 17. The week three antiviral release locations show the small initial release of antivirals prior to the rise in number of treatable cases. The locations in week three run north to south through the center of the state and are primarily rural counties. During the initial rise in treatable cases, week seven shows that the majority of the counties in Texas are released antivirals, including the heavily populated counties of Forth Worth, Dallas, San Antonio, and Houston. The large release in week seven may be a byproduct of releasing antivirals to the most populated counties in the state. The worried-well would consume too great a proportion if the large release of antivirals occurs earlier. If the large release to the populated counties occurred later, it would miss the rise in treatable people. Week nine continues the widespread distribution of antivirals, but withholds the release in the populated counties of San Antonio, Houston, and Fort Worth. Finally, week 25 shows the last few counties that are released antivirals at the end of the pandemic.

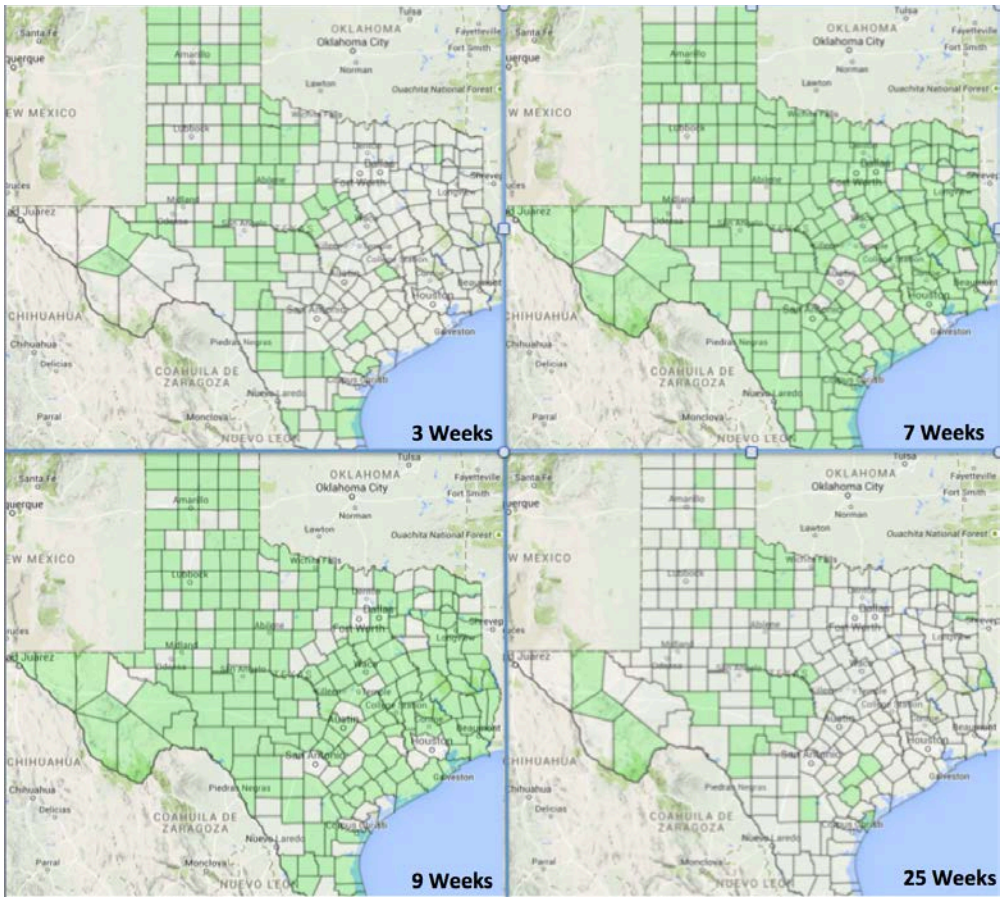

Figure 17. Week 3, 7, 9, and 25 statewide geographic antiviral release schedule snapshots in response to a1918-like random-origin influenza pandemic with unlimited antivirals maximizing lives saved. Antivirals are released to the counties in green (after TAVRS, 2015).

The antiviral release schedule to the base case influenza pandemic with unlimited antivirals only requires approximately 14 million antivirals which are used to treat a total of roughly 11 million treatable cases. Variations to the total number of antivirals available will be investigated further in later section of this chapter. Also, the release of the majority of the antivirals in bulk batches preceding the rise in treatable cases is an interesting trend. The base case release also releases all the antivirals in a relatively quick window because the disease spreads very rapidly throughout the Texas population.

B. VARIATIONS

In this section we vary four TAVRS input parameters, geographic origin, pandemic type, initial supply of antivirals, and objective optimization variation, to analyze the response of the resulting antiviral release schedule. The two variations of geographic origin are a border origin scenario and a population weighted origin scenario. Following that, the influenza type is varied to mimic a 2009-like influenza pandemic. The next variation examines limiting the number of antivirals available to 14 million, 6.1 million and 2 million. Finally, the objective function of the optimization program in TAVRS is changed to maximize hospitalizations avoided and QALYs saved.

1. Geographic Origin Variation

In our analysis, we will only vary one parameter at a time from the base case of a 1918-like random origin influenza pandemic with unlimited antivirals that maximizes the number of lives saved. Only the geographic origin will be varied in the following section. TAVRS varies the geographic origin of the influenza pandemic by *averaging a different set of treatable files* from the stochastic scenario library. The base case averaged the number of treatable persons in each time frame in each county and each population group from the 150 treatable person curves from 1918-like random origin influenza pandemic. The variation in geographic origin will change the set of treatable person curves that are averaged to a 1918-like border origin and then to a 1918-like population weighted origin.

a. Border Origin

In the Border origin variation, the geographic origin of the base case is changed to a Texas-Mexico border origin. The geographic location of the initial treatable cases, used to create the averaged treatable person curve, originates randomly but with greater frequency from the counties in Texas that share a border with Mexico. After the initial cases, the disease spreads without restriction throughout the counties in Texas. TAVRS maximizes the number of lives saved in the boarder origin variation to be 16,002 lives. TAVRS expects to save more lives in response to border-origin influenza pandemic. The graph in Figure 18 shows the TAVRS recommended time phased statewide release of antivirals in response to the base case scenario with a border origin. The chart is very

similar to the initial antiviral release schedule. It recommends the largest single release of 3.5 million antivirals at the seven week time period ahead of the rise in treatable persons curve. This initial peak release is followed by smaller peak releases at week ten and twelve.

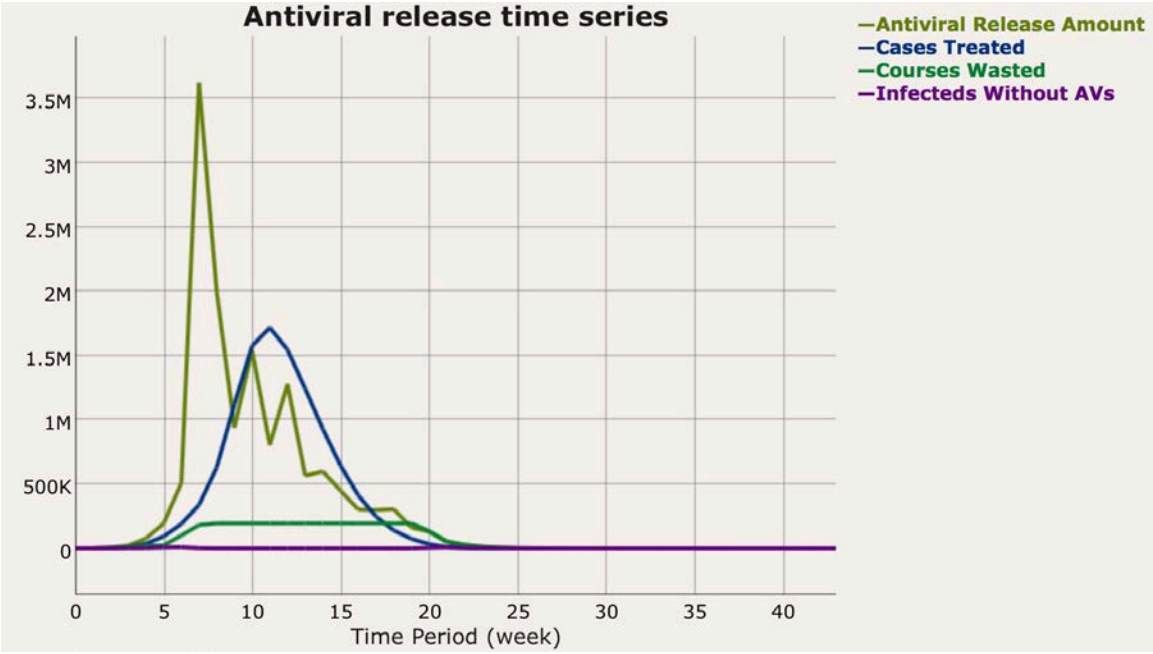

Figure 18. Time phased statewide antiviral release schedule in response to a1918-like border-origin pandemic with unlimited antivirals maximizing lives saved (after TAVRS, 2015).

Figure 19 shows that the county location snapshots of the antiviral release schedule with a geographic variation of the base case differ greatly from the location snapshots of the random-origin base case scenario. The same time period snapshots as the base case are shown: week three, seven, nine, and 25. The antivirals are distributed in week three to just the border counties. By week seven, almost all the counties in Texas receive antivirals including the population centers of Houston, Austin, Forth Worth, and Dallas. Week nine continues to release antivirals to the majority of counties in Texas, however the populations centers that received antivirals in week 5 are not released any new antivirals. Week 25 shows the last few rural counties in the center of Texas receive antivirals as the pandemic comes to a conclusion.

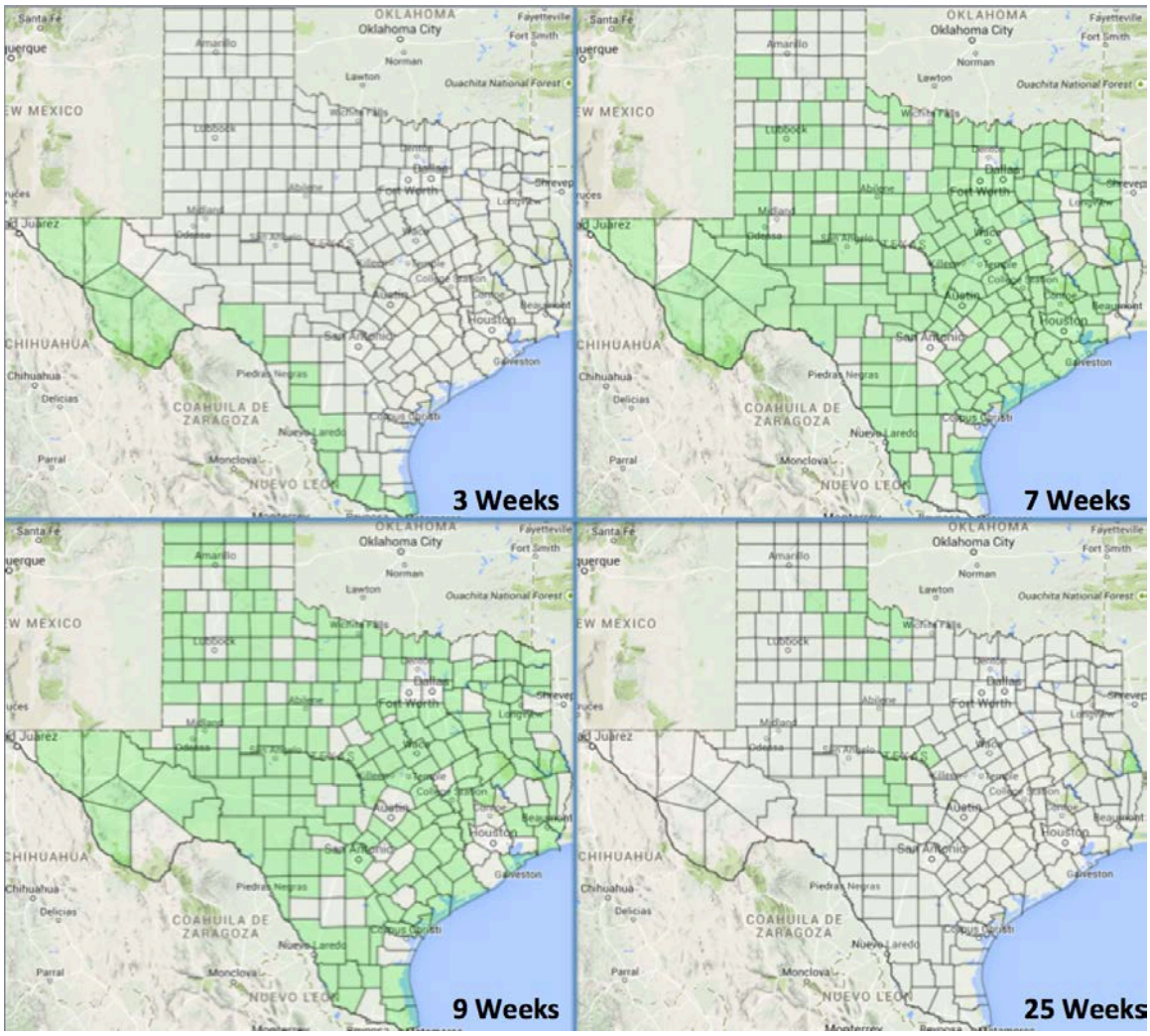

Figure 19. Week 3, 7, 9, and 25 statewide geographic antiviral release schedule snapshots in response to a 1918-like border-origin influenza pandemic with unlimited antivirals maximizing lives saved. Antivirals are released to the counties in green (after TAVRS, 2015).

While the geographic origin is varied, the time phased release of antivirals remains very similar to the base case time phased release schedule. The total number of antivirals released is still approximately 14 million. However, as one might expect, the recommended geographic antiviral release schedule for the border scenario varies greatly the recommended geographic antiviral release schedule for the base case.

b. Population-Weighted Origin

In the population-weighted variation, the geographic origin of the base case is changed to a random origin that is weighted to the larger population centers in Texas. The geographic location of the initial treatable cases, used to create the averaged treatable person curve, originates randomly but with more frequency in the counties with larger populations. TAVRS maximizes the number of lives saved this variation to be 15,508 lives. TAVRS expects to save fewer lives in response to border-origin influenza pandemic than a random origin. Figure 20 displays the TAVRS recommended time phased statewide release of antivirals in response to this variation than with a random origin. The chart is very similar to the base case antiviral release schedule; however, it recommends the largest single release of just over three million antivirals earlier, during week five, instead of week seven. This earlier initial peak in the release of antivirals correlates to a quicker rise in the number of treatable people. Also, the conclusion of the release of antivirals is earlier than the base case as well, at roughly 25 instead of 27 weeks.

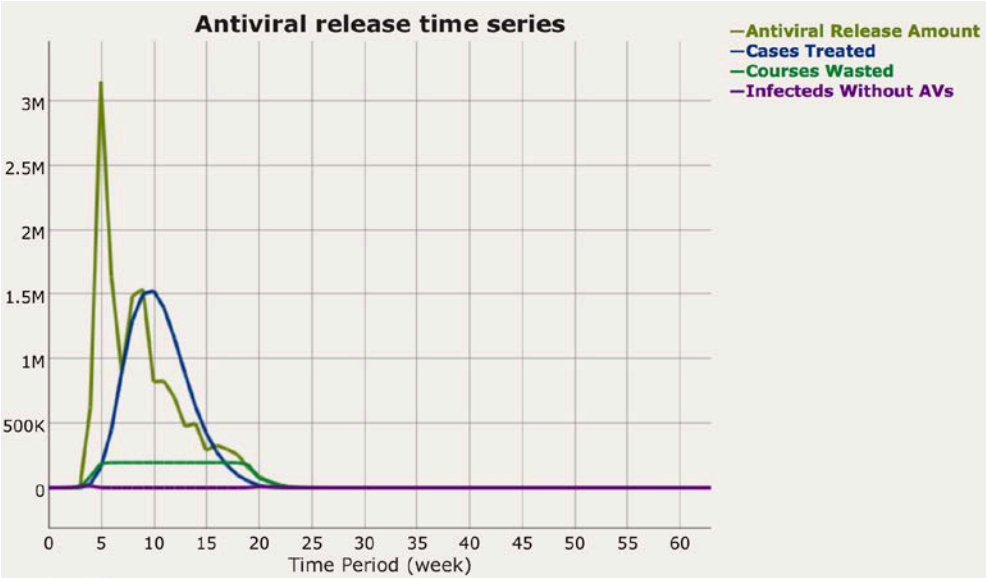

Figure 20. Time phased statewide antiviral release schedule in response to a1918-like population-weighted-origin pandemic with unlimited antivirals maximizing lives saved (after TAVRS, 2015).

The county snapshots from the population-weighted origin, shown in Figure 21, again vary from the random origin geographic distribution. Figure 21 shows the TAVRS recommended locations for the release of antivirals in weeks three, five, seven, and 25. These weeks are shown because the disease progresses a little quicker than the base case. The week 3 geographic release of antivirals only includes three rural counties in south-central Texas. Week five shows the rapid increase from week three to distribute the largest release of antivirals throughout the pandemic. The major population centers of Austin, Houston, Dallas, and San Antonio are released antivirals in this time frame. Week 7 releases antivirals to a similarly large number of counties in the state, but with slightly less number of antivirals. Week 25 shows the last few counties to receive antivirals as the pandemic comes to a conclusion.

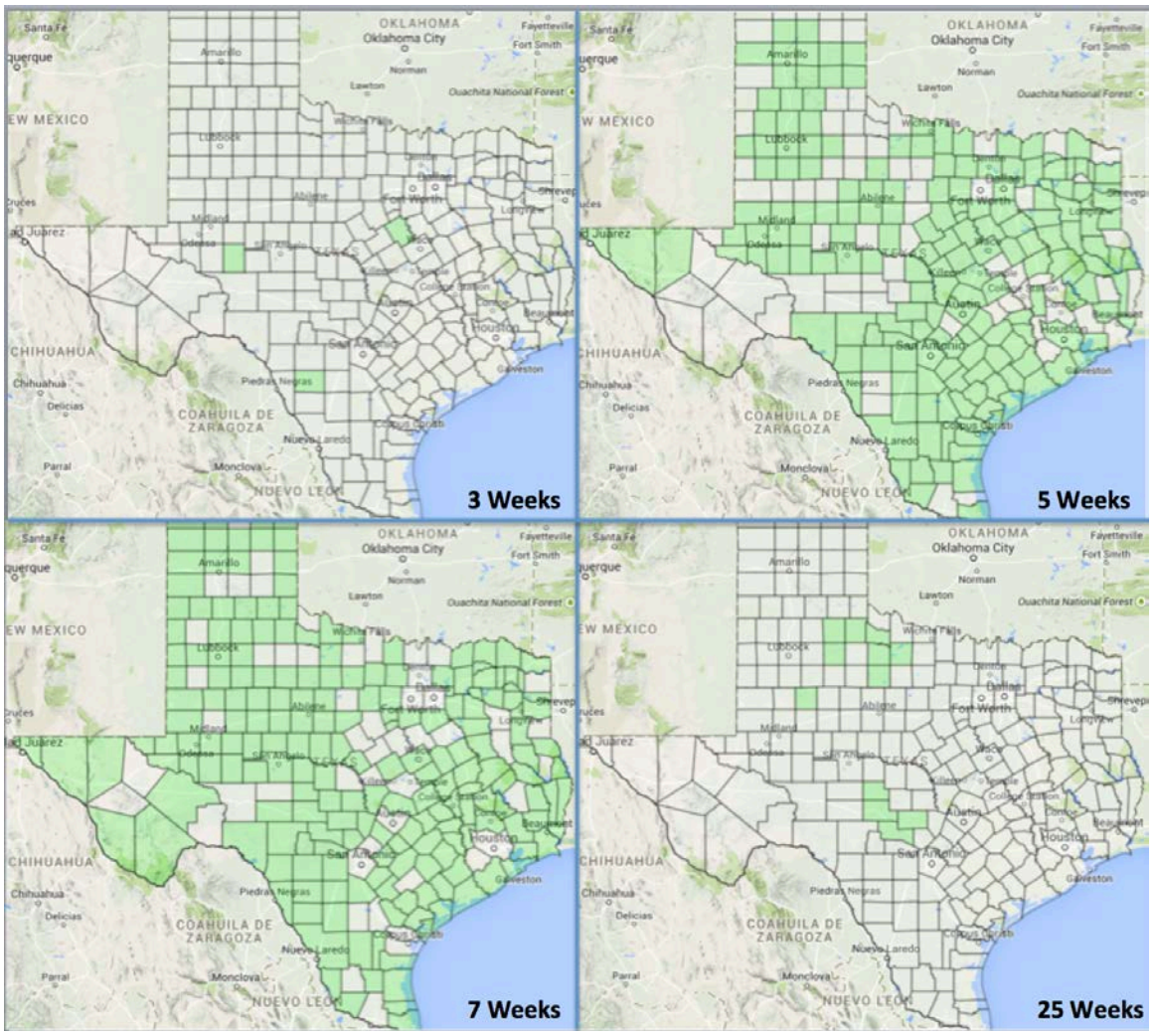

Figure 21. Week 3, 5, 7, and 25 statewide geographic antiviral release schedule snapshots in response to a 1918-like population-weighted-origin influenza pandemic with unlimited antivirals maximizing lives saved. Antivirals are released to the counties in green (after TAVRS, 2015).

Overall, the variation of the geographic origin of 1918-like influenza results in a more rapid rise in treatable people, leading to the faster distribution of antivirals throughout the state. This could be due to the population-weighted origin of the pandemic in the larger population counties, which usually have a higher population density. The closer contact in denser populations could account for the quicker rise in the number of treatable people and the subsequent quicker TAVRS recommended release of antivirals.

The geographic distribution of the release of antivirals is similar to the base case but accounts for the quicker progression of the pandemic.

2. Pandemic Variation (2009-Like Pandemic)

The next TAVRS input parameter to be varied from the base case is the historic influenza pandemic strain. Recall that that influenza strains in TAVRS are categorized into historic pandemic influenza strains, each of which has specific ranges of pandemic parameters. TAVRS averages only the set of treatable person curves that were created with the disease parameters from the historic influenza pandemic strain selected by the user. TAVRS optimizes the antiviral release schedule with this specific average treatable persons curve. Our analysis only changes the pandemic strain from the base case, from 1918-like to 2009-like, while keeping all other parameters the same.

Figure 22 shows the time phased statewide antiviral release schedule in response to a 2009-like pandemic with a random origin pandemic with unlimited antivirals that maximize lives saved. The release schedule is similar to the base case that responds to 1918-like pandemic influenza because the timing of the largest single release, at week 11, precedes the rapid rise in treatable persons. However, the 2009-like pandemic influenza does not spread as rapidly as the 1918 pandemic influenza resulting in a prolonged epidemic that is less severe. The total treatable persons do not exceed 8 million and the total TAVRS recommended antivirals released is just over 12 million with no single release exceeding 2 million antivirals. As one would expect, both metrics support the observation that the 2009-like influenza pandemic was a much more mild strain than the 1918-like Spanish flu. TAVRS maximizes the number of lives saved in the 2009-like variation to be 195 lives. Fewer people become infected and therefore cannot be treated and saved so the number is much less than Spanish flu influenza pandemic.

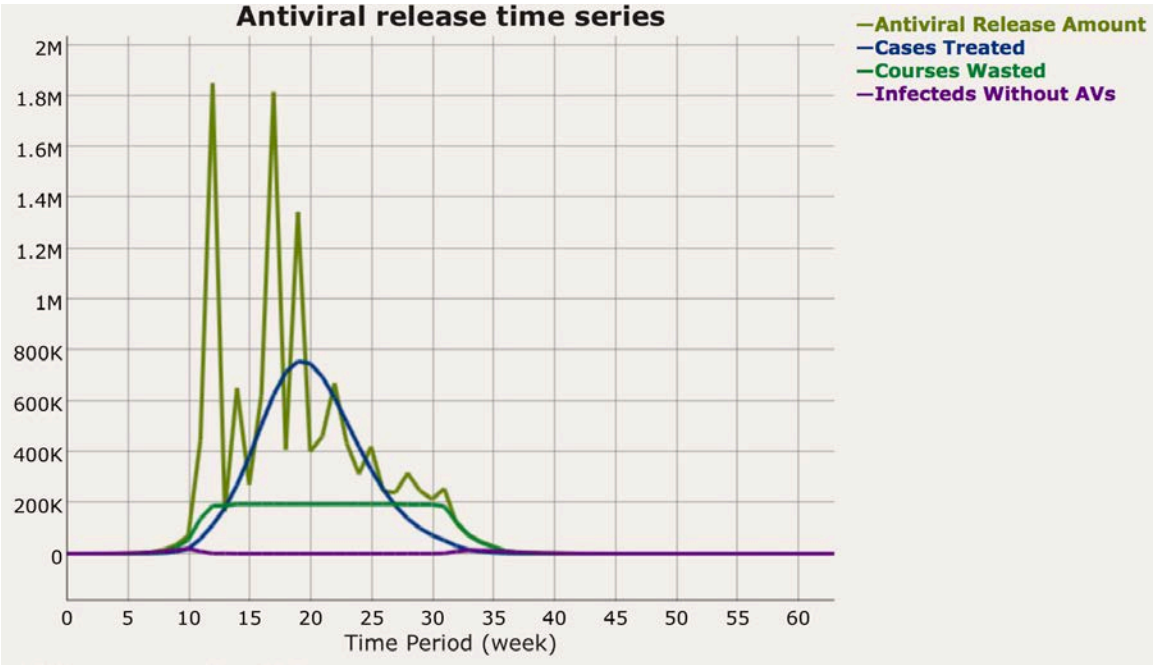

Figure 22. Time phased statewide antiviral release schedule in response to a 2009-like random-origin pandemic with unlimited antivirals maximizing lives saved (after TAVRS, 2015).

The geographic distribution of the antiviral release schedule was similar to the base case geographic distribution extended over the longer duration and releasing fewer antivirals. The border and population weighted geographic origin variations demonstrated the same county snapshots at later times than the 1918-like influenza pandemic. There are a greater number of releases, with fewer antivirals released in each, as demonstrated by the greater number of spikes in the chart from Figure 22. Overall TAVRS recommends a milder response to the influenza pandemic that has been varied to mimic the 2009 swine flu.

3. Antiviral Release Variation

The total number of antivirals available to be released is the next TAVRS parameter to adjust. The antiviral release schedule to the base case scenario, the 1918-like random-origin influenza pandemic, recommended that only 14 million antivirals be released even though the optimization program could release up to 30 million. According to TAVRS, releasing more than 14 million antivirals does not improve the lives saved.

The next section examines three variations in the total number of antivirals available to TAVRS to release: 14 million, 6.1 million, and 2 million. 14 million total antivirals are expected to provide the same reduction in deaths as the release of 30 million antivirals. 6.1 million total antivirals available is an estimate of the most likely antiviral scenario. The actual total number of antivirals available is not released to the public. Finally, the 2 million total antivirals scenario creates a limited antiviral scenario.

a. 14 Million

TAVRS recommends a very similar time-phased statewide antiviral release schedule after reducing the total antivirals available to 14 million. TAVRS optimizes the release of antivirals for a maximum number of 26,551 lives saved, the same optimized lives saved if 30 million antivirals were available. All 14 million antivirals are released over roughly a 25-week period. The largest single release of antivirals occurs during week 7 and similarly precedes the rise in treatable persons. The cases treated, courses wasted and infected without antivirals have similar trends to the base case as well. As expected, it appears TAVRS needs only 14 million antivirals to accomplish the same release schedule as the base case.

b. 6.1 Million

Restricting the total number of antivirals available to 6.1 million forces TAVRS to adjust the time phased antiviral release schedule, shown in Figure 23. TAVRS optimizes the antiviral release schedule for a maximum of 15,705 lives saved. The antivirals are released only after a significant increase in the number of infected without antivirals. The number of infected without antivirals begins to increase at week 5, after which, at week seven, TAVRS recommends a stark increase in the number of antivirals released. The number of infected without antivirals, the purple line, peaks at a little over one million during the 10-week mark, as the number of antivirals released quickly increases. The antivirals released peaks at 11 weeks distributing over 2.2 million at once. This point marks a rise in the number of cases treated with antivirals and a decrease in the number of infected without antivirals.

The chart from Figure 24 shows the cumulative values of the curves from the chart in Figure 23. The number of cases treated is slightly less than the number of infected without antivirals, which in turn, is slightly less than the number of antivirals released. The geographic distribution of the release schedule (not shown) show that TAVRS delays releasing antivirals to the large population centers in the random origin scenario. San Antonio, Dallas, and Fort Worth are not released antivirals until week 11 and Houston does not receive antivirals until week 13. In a reduced antiviral situation TAVRS delays the release of antivirals. Limiting the number of antivirals available to 6.1 million highlights the necessity of a very specific release schedule.

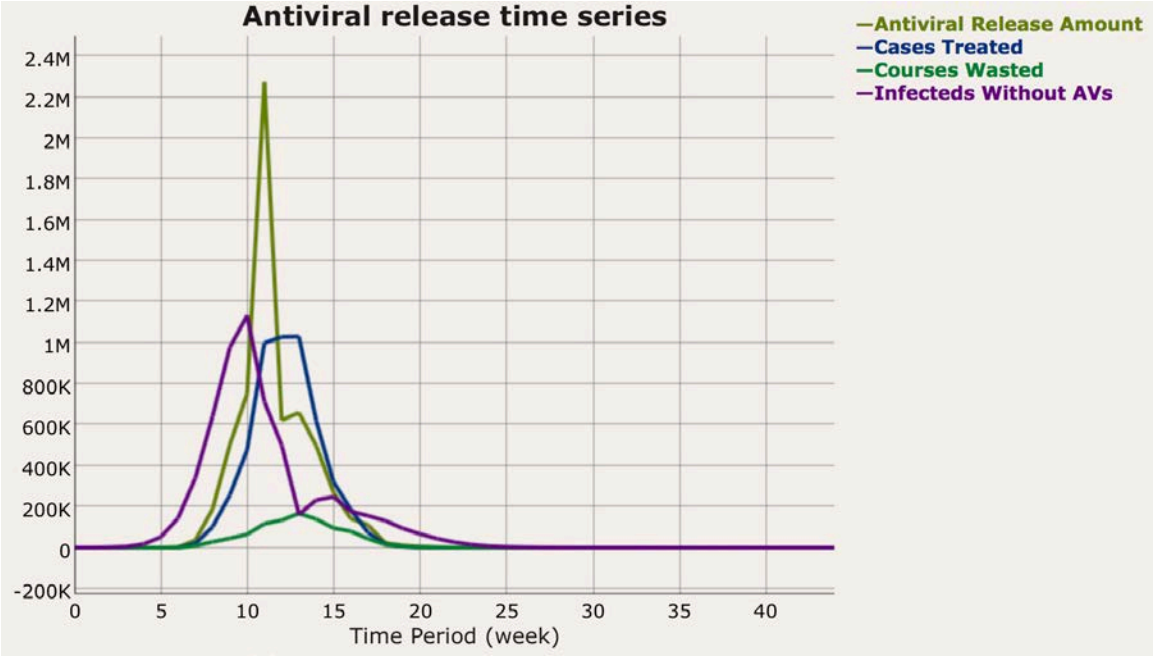

Figure 23. Time phased statewide antiviral release schedule in response to a 1918-like random-origin pandemic with 6.1 million antivirals available maximizing lives saved (after TAVRS, 2015).

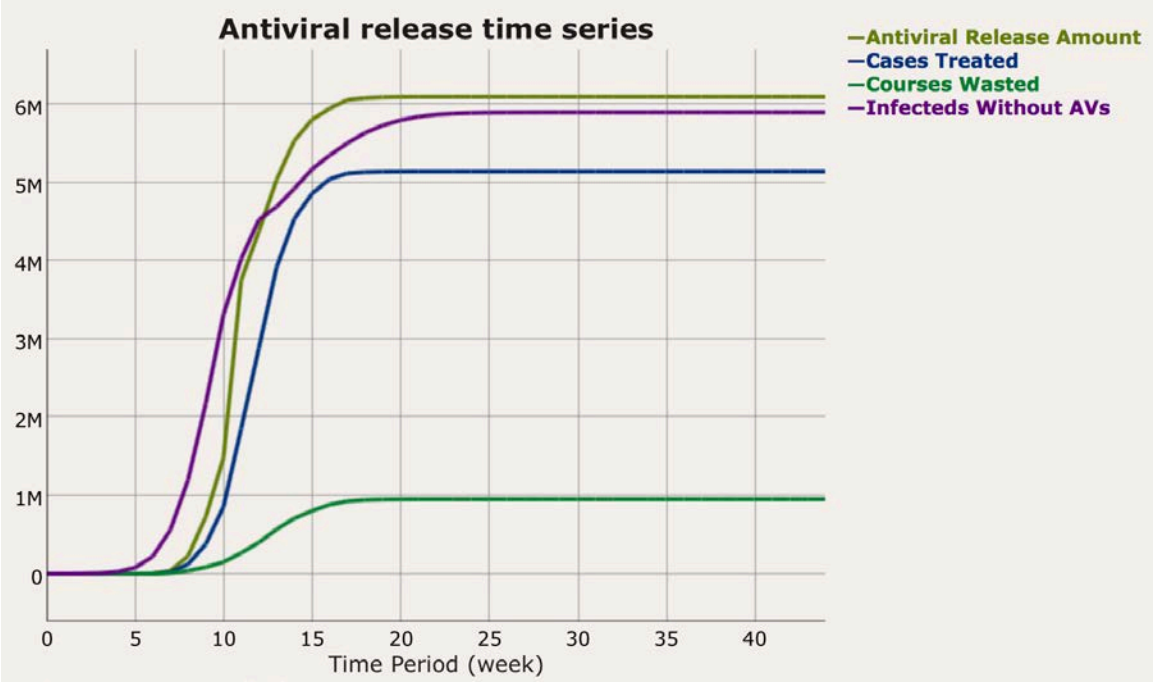

Figure 24. Time phased cumulative statewide antiviral release schedule in response to a 1918-like random-origin pandemic with 6.1 million antivirals available maximizing lives saved (after TAVRS, 2015).

c. 2 Million

The further reduction of the total antivirals available in TAVRS to two million creates the time phased antiviral release schedule shown in Figure 25. TAVRS optimizes the release schedule for a maximum of 5,364 lives saved. The number of cases treated never exceeds the number of infected without antivirals throughout the course of the pandemic. TAVRS recommends the release in the small number of antivirals during week 11, only after a large increase in the number of infected without antivirals, which eventually peaks during week 10 at 1.4 million. The large population centers in Texas are never released antivirals. When antivirals are extremely limited, TAVRS recommends delaying their release even later and does not recommend distributing to the counties with the largest populations.

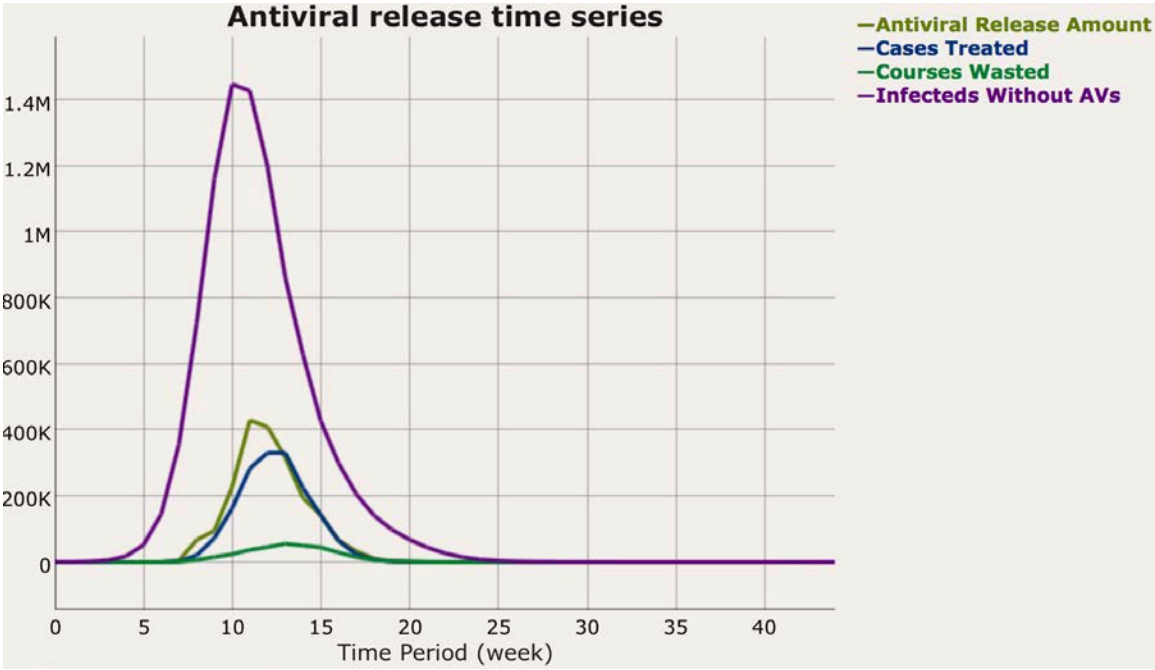

Figure 25. Time phased statewide antiviral release schedule in response to a 1918-like random-origin pandemic with 2 million antivirals available maximizing lives saved (after TAVRS, 2015).

4. Objective Variation

The final TAVRS input parameter to be varied is the objective function. The base case uses the maximization of the number of lives saved to create an optimal antiviral release schedule. In this section, the other two objective functions are examined: the minimization of hospitalizations and the maximization of QALYs. A TAVRS antiviral release schedule with the objective function changed to maximize the number of hospitalizations avoided does not appear to drastically change the release schedule. The largest single release of almost 4 million antivirals occurs immediately before the steep rise in treatable individuals during week 7. The number of hospitalizations avoided is determined to be a maximum of 1,130. This could lead to a significant savings for hospitals. After adjusting the optimization function to maximize QALYs, the TAVRS optimized antiviral release schedule appears to have no significant change in when and where it released antivirals. This could be a product of having a relatively consistent age distribution across each county.

C. SIMULATION COMPARISON

To further evaluate the effectiveness of TAVRS, we use the optimized antiviral release schedule in a completely different model. We implement the TAVRS optimized antiviral schedule in the Texas Pandemic Flu Simulator (TPFS) in order to compare our expected total lives saved from TAVRS to the total lives saved in the TPFS. We evaluate six different pandemic scenarios that vary two pandemic strains with three geographic origins. We also compare the effectiveness of a simpler population-proportionate antiviral release schedule against the TAVRS optimized antiviral release schedule with the same scenarios in TPFS. Through this test, we determine if TAVRS performs as well as it advertises and how well it performs compared to another antiviral release schedule.

The TPFS and TAVRS are different models with expressly separate purposes. TAVRS incorporates the optimization program formulated in Chapter III to release antivirals that maximize a specific benefit. It optimizes only a single intervention, antivirals, and only produces an antiviral release schedule. We can only examine the lives saved metric because the TPFS outputs the total number of deceased but not the number of hospitalizations and number of QALYs.

TPFS is a disease-spread model, as mentioned in Chapter II, designed to simulate the progression of an influenza pandemic. It incorporates many different pandemic and intervention inputs and provides an extensive number of output parameters through a mass action compartmental model. The TPFS was originally used in this thesis to simulate pandemics in Texas *without* any antiviral intervention in order to create the geo-temporal layered average treatable persons data for use in our optimization model. In this section, we use TPFS to find the total lives saved by comparing the number of deceased individuals throughout a pandemic *with* antiviral release schedules to the number of deceased individuals without incorporating antiviral releases. There is no guarantee that the number of expected lives saved in TAVRS is remotely near the comparison of deceased individuals in TPFS because the models are completely different.

We assemble six scenarios in the TPFS, shown in Table 10. Scenarios one through three simulate the 2009-like Swine flu originating from the three geographic

origin options. Scenarios four through six do the same for the 1918-like Spanish flu pandemic. Each scenario initiates the pandemic in five counties that depend on the geographic origin. In the truly random geographic origin, the pandemic originates in three rural counties spread throughout the state (Tom Green, Bowie, and Potter) as well as two populated counties (Harris and El Paso). In the Border origin scenario, the pandemic originates in five boarder counties, including one heavily populated county: El Paso. In the population-weighted origin, all five counties are heavily populated counties in Texas.

Table 10. Scenarios for the TPFS lives-saved comparison.

Scenario	Pandemic	Random Selection Weight	10 initial cases in each county
1	2009-like	Random	Tom Green, Harris, El Paso, Bowie, Potter
2		Border	Webb, El Paso, Cameron, Maverick, Val Verde
3		Population	Harris, Dallas, Texas, Bexar, El Paso
4	1918-like	Random	Tom Green, Harris, El Paso, Bowie, Potter
5		Border	Webb, El Paso, Cameron, Maverick, Val Verde
6		Population	Harris, Dallas, Texas, Bexar, El Paso

Each scenario in Table 10 compares the average total deaths throughout the pandemic without antivirals released to the average total deaths with two different antiviral release schedules: a population weighted population distribution of antivirals and the TAVRS optimized antiviral release schedule. The average total deaths for each antiviral release schedule in each scenario were calculated through three runs in the TPFS for a total of 54 simulation runs. The TPFS does not provide for command line access therefore all inputs must be made in the GUI limiting the speed and efficiency of multiple runs. This produces a low sample size that limits our conclusions. The population weighted release schedule provides all of antivirals to each county, proportioned by population, during the initial week of the pandemic. Each schedule simulates the release of 6,100,000 antivirals. This analysis will produce the average number of lives saved using antivirals released with the two different schedules.

1. 2009-Like Influenza Pandemic Mortality Comparison

The results for a 2009-like pandemic reveal some surprises. Without antivirals, the average number of people to die from a 2009-like pandemic influenza is 3,150 people. Columns one and two in Table 11 show the average lives saved with the population-proportionate antiviral schedule and with the TAVRS optimized release schedule, respectively, after three runs each. The population proportionate schedule outperforms the TAVRS schedule in two of the three scenarios; however, no scenario yields a statistically superior release schedule. Even in the 2009-random origin scenario, which saves approximately 270 more lives, the difference between the two release schedules' lives saved is not statistically significant on the 90 percent confidence level, as shown by the bracketed confidence intervals in Table 11. This is due to the small sample size of simulation runs. Efficiently running many simulations is included in the follow on work discussed in Chapter V. Note that antivirals saved less than 10 percent of the total deaths in all situations. Recall from Chapter I that the purpose of antivirals is to provide immediate intervention along with social distancing until a vaccine can be produced. Antivirals are just one tool in an intervention strategy.

The third column of Table 11 contains the optimal lives saved in each scenario according to the optimization program in TAVRS. Even though TAVRS and TFPS are separate models, if our optimization model adequately reflects the dynamics, then we expect columns 2 and 3 to be similar. TAVRS maximizes the lives saved in each 2009-like influenza pandemic scenario to be roughly 200, which falls into the 90 percent confidence interval on the TAVRS release schedule TPFS results. While the average TPFS lives saved with the TAVRS antiviral release schedule approaches the TAVRS maximized lives saved in each scenario, the population-proportional release schedule average lives saved actually outperforms it in the random scenario. This may be due to inherent fundamental differences in each model. Also, the 2009-like strain of influenza is mild enough where the majority of people needing (and not needing) antivirals have access to them. The population-proportionate release of antivirals evenly distributes antivirals that inadvertently provide more effective treatments in addition to more ineffective treatments, saving more than the TAVRS "optimal" lives.

Table 11. Lives-saved comparison for 2009-like influenza pandemic.

Scenario	Average Simulated "Lives Saved" Population-Proportional Release Schedule [90% CI]	Average Simualted"Lives Saved" TAVRS Release Schedule [90% CI]	TAVRS optimized "Lives Saved"
2009-Border	174 [251, 97]	154 [281, 28]	211
2009-Random	272 [320, 225]	184 [231, 136]	195
2009-Population	138 [186, 90]	144 [272, 15]	193

2. 1918-Like Influenza Pandemic Mortality Comparison

The 1918-like pandemic, a much more severe influenza than the 2009 strain, yields a much different comparison. To put the lifesavings in perspective, without antivirals the 1918-like average death toll is approximately 270,000, roughly 90 times greater than the average death toll from the 2009-like pandemic. Table 12 shows that a TAVRS optimized antiviral release schedule consistently outperforms the population proportionate distribution of antivirals. The difference between the lives saved by the TAVRS release schedule and the population proportionate release schedule is statistically significant on the 90 percent confidence level, as shown by the confidence intervals in columns one and two. The TPFS results show the TAVRS optimized antiviral release schedules save on average over three to four times as many lives as the population proportionate distribution of antivirals in each scenario. That means over 10,000 more lives are saved on average with the TAVRS optimized antiviral release schedule. In the presence of a severe strain of influenza, the value of every antiviral is important; therefore, the release schedule must be exceptionally precise in targeting the treatable population.

In column 3, the TAVRS optimization program advertises a maximum lives saved of between fifteen thousand five hundred and sixteen thousand depending upon which geographic region the pandemic begins. The TAVRS antiviral release schedule's performance in the TPFS comes close to saving as many lives on average as the expected lives saved from the TAVRS optimization program, approximately 1,000 to 1,500 less in each scenario. The TAVRS maximized lives saved is within the 90 percent confidence interval from the TPFS average lives saved using the TAVRS antiviral release schedule

in two of the three scenarios, and outside of the confidence interval on the third by just 300 lives. The performance of the TAVRS release schedule in the TPFS matches the TAVRS predicted lives saved very well.

Table 12. Lives-saved comparison for a 1918-like influenza pandemic.

Scenario	Average Simulated "Lives Saved" Population-Proportional Release Schedule [90% CI]	Average Simualted"Lives Saved" TAVRS Release Schedule [90% CI]	TAVRS optimized "Lives Saved"
1918-Border	4640 [5514, 3766]	15620 [16582, 14658]	16003
1918-Random	3427 [5091, 1762]	14281 [15829, 12733]	15706
1918-Populaiton	4044 [4725, 3362]	14383 [15209, 13556]	15508

The 2009-like influenza pandemic was much milder than the 1918-like pandemic. When antivirals are not in limited supply, a simple population proportionate distribution works as well as the TAVRS optimized release schedule. However, in the presence of a severe pandemic, the population proportionate distribution greatly limits the effectiveness of the antivirals. In response to a severe pandemic, it is important to optimize the limited supplies until vaccines are produced. A TAVRS optimized release schedule will save a significantly greater number of lives during a severe pandemic.

V. CONCLUSION

We have developed an optimization program that is implemented in TAVRS to provide the optimal antiviral release schedule to decision makers. Specifically, our optimization program creates a geo-temporal antiviral release schedule to maximize the antiviral benefit to the population of Texas. Possible benefits include lives saved, hospitalizations avoided, and QALYs saved. The program incorporates three different dimensions: time, location, and age-demographic groups known as population groups. The population groups include 20 categories that combine 5 age groups (0-4, 5–24, 25–49,50-65, and 56+) with four demographic groups (low-risk, high-risk, first responders, and pregnant women) well as a category for the worried-well, a group with individuals that think they are infected with influenza but in fact are not.

The optimization program includes three different data inputs: treatable persons, antiviral benefit, and antivirals available. Treatable persons, individuals that are symptomatic for less than 48 hours, are a product of the Texas Pandemic Flu Simulator. The optimization program targets a treatable population with the geo-temporal release of antivirals. In order to implement the optimization program in TAVRS, we averaged a set of treatable persons for geographic origins of influenza as well as specific historical strains of pandemic influenza. For example, using our optimization program in TAVRS decision makers can determine the optimal antiviral release schedule for a border-origin, 2009-like influenza strain.

We formulate a mixed integer linear program to optimize the antiviral release schedule. The model assumes that the spread of the influenza is independent of the antiviral release. Any antivirals received by the worried-well will have a negative impact on the benefit of the antiviral release. Also, all individuals in a population group will have the same benefit if they receive antivirals.

We first consider a base case scenario, which consists of a 1918-like random-origin influenza pandemic with unlimited antivirals. The release schedule maximized the lives saved to roughly 26,500 by releasing a large amount immediately before the rise in

treatable people. Although 30 million antivirals are available, TAVRS releases only 14 million. Antivirals are released to the highest populated counties during the weeks that precede the fast rise in treatable population. Antivirals released earlier may be consumed by the worried-well and antivirals released later are not available for the rise in treatable people.

We next examined several variants from the base model. When the pandemic originates near the border, the optimal schedule releases antivirals to the counties immediately prior to when the disease significantly spreads to them. When the pandemic originates in a highly populated county, the pandemic can spread quickly. A less virulent pandemic strain generates an extended release schedule duration and fewer antivirals released. A smaller supply of antivirals results in a delay in the release of the bulk of the antivirals. Finally, the specific objective function (lives saves, hospitalization, QALYs) had no apparent impact of the release schedule of antivirals.

Our analysis concludes with a comparison of the lives saved between the TAVRS antiviral release schedules and a simpler population-proportionate population distribution. The comparison found that in response to a mild pandemic, like the 2009 swine flu, the population-proportionate antiviral release schedule worked comparably the TAVRS antiviral release schedule. However, in response to a severe strain of influenza, like the 1918 Spanish flu, the TAVRS antiviral release schedule performed drastically better saving roughly 10,000 more lives, three to four times greater, than the population-proportionate release schedule.

There is much room for follow-on work. The optimization model can be improved by creating a truly stochastic optimization program. Our model uses the average of a set of stochastically created treatable person data. A truly stochastic program would use many treatable persons runs to robustly optimize the release of antivirals. Also, the Texas pandemic Flu Simulator's could bypass the guided user interface (GUI) to input parameters and release schedules that run many scenarios efficiently. Currently, the parameters into the TPFS are only input manually. One could input parameters through command line prompts for more statistically relevant analysis of the TAVRS antiviral release schedules. Finally, the optimization program could incorporate the

coordination of several pandemic interventions working together. While the optimization of antivirals is important, it loses the bigger picture. Decision makers have to optimize several tools in order to determine the best intervention strategy. A holistic optimization would include the current policy of releasing antivirals and implementing social distancing until vaccines are developed and distributed. The interactions of several interventions are complicated but this would reflect a more realistic strategy from the state of Texas.

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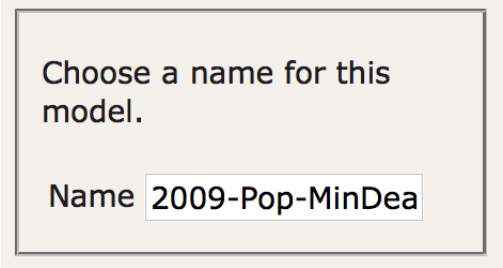
APPENDIX. TAVRS-GUIDED TUTORIAL

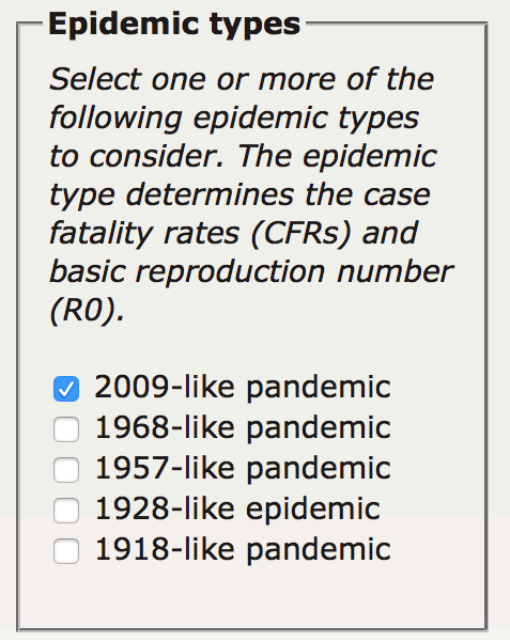
In this chapter, a TAVRS tutorial shows a step-by-step process to create and analyze an antiviral release schedule. The model is created for a 2009-like influenza epidemic that originates from the population centers in Texas and seeks to minimize deaths by distributing antivirals. The model is known as "2009-pop-MinDeaths."

First log on with a username and password to the Texas Pandemic Flu Toolkit at http://flu.tacc.utexas.edu. Click on "Texas Antiviral Release Scheduling." From there three options present themselves on upper right side of the main page: "New Model," "Current Model," "Archive." Select "New Model."

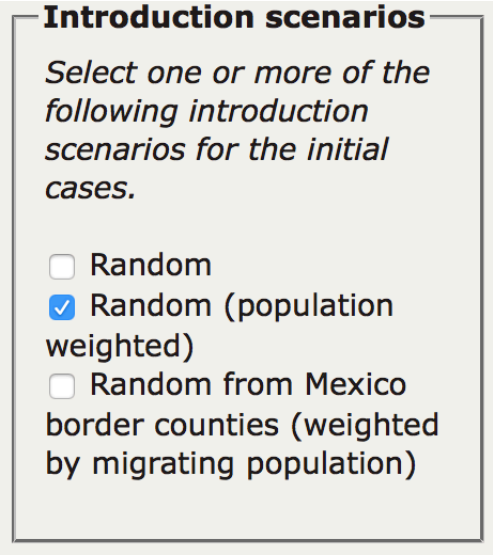
The first step is to *name the model*. In this case the name of the model represents the scenario that is modeled. In the text box write "2009-Pop-MinDeaths."



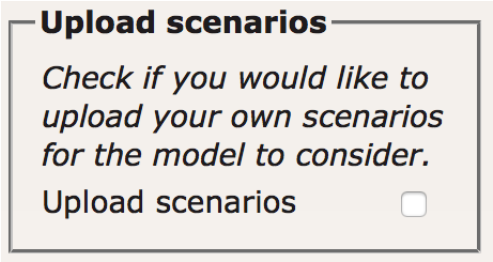
The next step is to select the epidemic type. This determines the basic reproduction number and the case fatality rate. The decision maker can select from just one epidemic type to up to all 5 scenarios. If the characteristics of the epidemic are well known, one may choose to select just a single one. If little information is known about the epidemic it may be more prudent to select all five epidemic types. In this case select "2009-like pandemic."



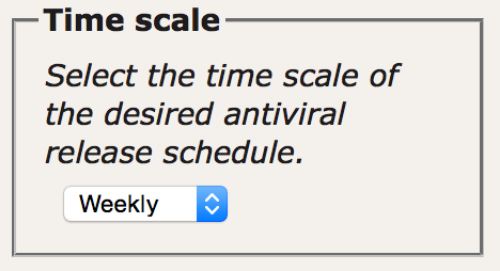
Scrolling down, the next step is selecting the introduction scenarios. This pertains to the geographic location of the initial cases of the pandemic. One can choose between "Random," "Random (population weighted)," and "Random from Mexican border counties (weighted by migrating population)." Choose "Random (population weighted)." Between the geographic conditions and the epidemic type, TAVRS will select the corresponding progression scenarios in the background. For our case it will use 150 progression scenarios.



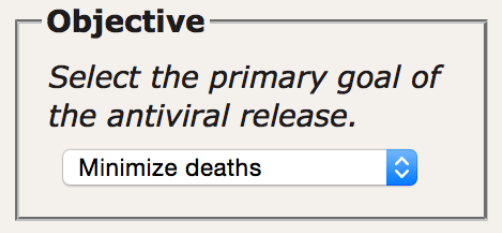
If one has a particular set of disease parameters and initial location, a unique scenario can be uploaded. The output from the Texas Pandemic Flu Simulator provides a set of treatable files that TAVRS will use to optimize the time phased antiviral release schedule. In this case do not upload scenarios.



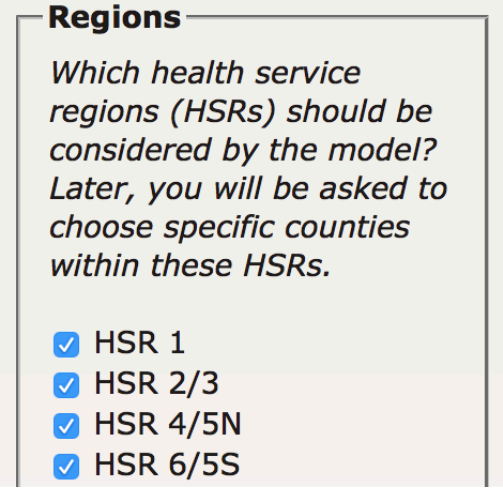
The next option is to determine the time scale to be used for antiviral distribution. TAVRS will use this selection to set the time period at a constant length. The dropdown menu allows the user to select either weekly, biweekly, or monthly. Select the weekly option for our scenario.



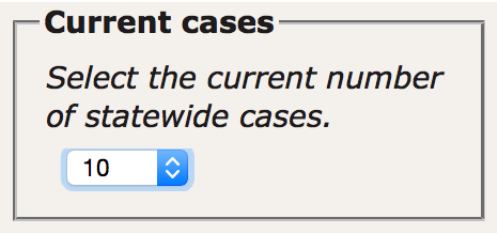
The next step is very important. TAVRS objective is selected from a dropdown menu. The choices the decision maker has are “minimize deaths,” “minimize hospitalizations,” and “maximize life years saved.” Select “minimize deaths” for this scenario.



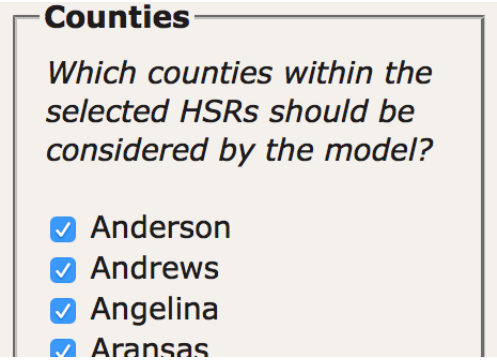
TAVRS also allows the user to select the health service region (HSR) in which he wants to investigate. The user may select from one HSR to all of them. TAVRS is run on the whole state of Texas still, but just the HSR of interest is reported.



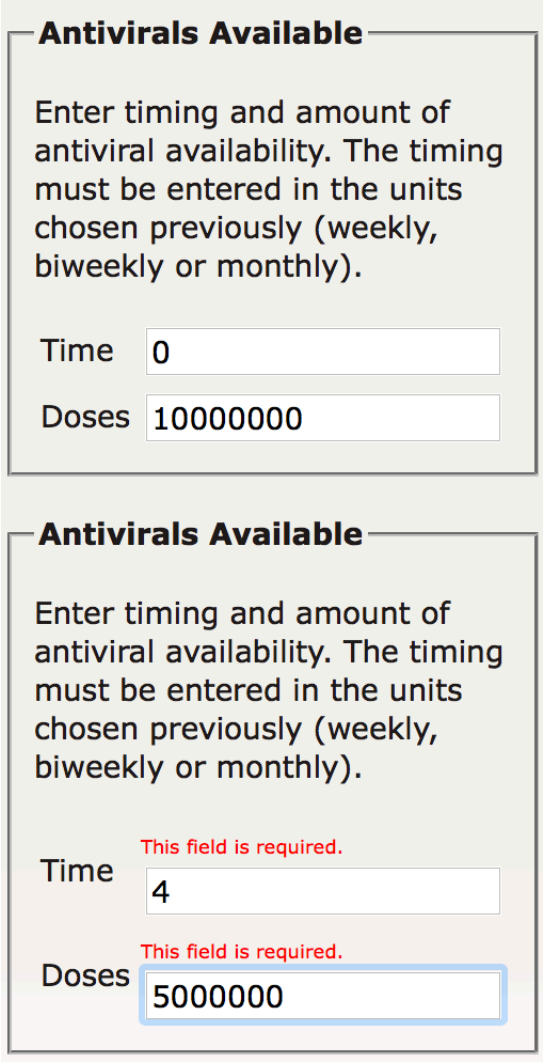
The decision maker also selects the current number of cases statewide throughout Texas. Most often the decision make is modeling the epidemic after the statewide cases has hit a certain threshold. This is usually on a larger order of magnitude. The option still exists for the user to select a small number of cases and determine the release schedule of antivirals from there.



The counties selection allows the decision maker to further narrow the release schedule that is displayed on the screen.



Finally, the decision maker inputs the number of antivirals available and at what time they become available. This input will most likely include an initial stockpile of antivirals as well as additional amounts provided by the CDC's SNS. It is important to remember what units the time periods are in because that will determine how many time periods the user will input.



Following this last step, the online window will change to the "Archive" tab. The scenario that was just created is assigned a job number and the text below it will keep the user posted of the progress. In around 5–10 minutes a TAVRS will produce a antiviral release schedule tailored to the scenario just created.

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